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Rec'd PCT/PTO 12 FEB 2002

Phenanthroline-7-one derivatives and their therapeutic applications

The present invention relates to pharmaceutical compositions based on polyaromatic compounds of use in particular as antitumour medicaments.

In 1999, cytotoxic treatments (chemotherapy) used to reduce the size of cancerous tumours, to suppress the development of the tumour process or indeed even, in still too few cases, to eliminate clumps of cancer cells and the risk of metastases, combine chemical substances which have been recently introduced with others which have been used for several decades. For example, 5-fluorouracil (5-FU), recognized for nearly 40 years as one of the most active treatments for colorectal cancer, can be replaced by one or other of the specific inhibitors of topoisomerase I (irinotecan or topotecan) when the tumour is no longer sensitive to 5-FU. More generally, the therapeutic arsenal available for treating colorectal tumours will also be enriched with the availability of oxaliplatin, novel in situ "donors" of 5-FU or selective inhibitors of thymidylate synthetase. This coexistence is not limited to the treatment of colorectal cancers since, in addition, the chemotherapy of breast, ovarian and lung cancers now makes wide use of the family of taxane derivatives (paclitaxel, docetaxel). The need for more effective and better tolerated treatments, thus improving the survival and the quality of life of the patients, is imperative since, still taking the example of colorectal tumours, it has been estimated (S.L. Parker, T. Tong, S. Bolden *et al.*, CA Cancer J. Clin., 1997) that, in the United States alone, over 131 000 new cases were diagnosed in 1997, 54 000 of which were responsible for the death of the patient. It is the awareness of this situation which has prompted the inventors to focus their attention on a family of

studied, identified in Ascidians of warm seawaters, to develop a novel medicinal chemistry intended to select synthetic compounds derived from a design/chemical modulation study and having significant therapeutic cytotoxic activity.

The seas and oceans which cover more than 70% of the surface of the globe harbor marine plants and sponges whose gradual systematic pharmacognosic study shows that these living species can contain complex alkaloids that have advantageous pharmacological properties. For example, the sponges *Cryptotheca crypta* and *Halichondria okadai* have been the subject of extensive studies since the discovery of the presence, in their cells, of cytarabine or of halichondrine B. This is likewise the case for the family of tunicates, since the isolation of aplidin from the tunicate *Aplidium albicans* which lives in the Balearic islands (Spain). Alkaloids of tetrahydroisoquinolone structure have been isolated from the ascidian *Ecteinascidia turbinata*. Among these, ecteinascidin-743 has been the subject of extensive preclinical studies (E. Igbicka et al., NCI-EORTC symposium, 1998; Abst. 130 p. 34), and also clinical trials intended to define its therapeutic potential as an anticancer drug (A. Bowman et al., NCI-EORTC symposium, 1998; Abst. 452 p. 118; M. Villanova-Calero et al., NCI-EORTC symposium, 1998; Abst. 453 p. 118; M.J.X. Hillebrand et al., NCI-EORTC symposium, 1998; Abst. 455 p. 119; E. Citkovic et al., NCI-EORTC symposium, 1998; Abst. 456 p. 119). Novel pentacyclic acridine derivatives have also been the subject of pharmacochemical studies (D.J. Hagan et al., J. Chem. Soc., Perkin Transf., 1997; 1: 2739-2746).

Another natural alkaloid of marine origin, ascididemin, has been extracted from the tunicate *Didemnum sp.* (J. Kobayashi et al., Tetrahedron, lett. 1988; 29: 1177-80) and from the ascidian *Cystodytes dellechiajei* (I. Bonnard et al., Anti-cancer Drug design 1995; 10:

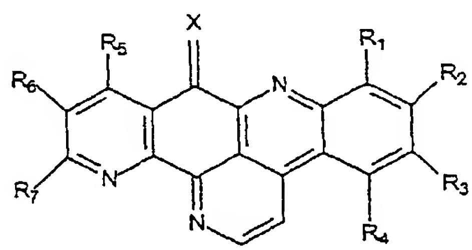
333-46). Ascididemin possesses antiproliferative properties demonstrated on the model of mouse leukemia (lines P388 or L1210) and described by F. Schmitz et al. (J. Org. Chem. 1991; 56: 804-8), B. Lindsay et al. (Bioorg. Med. Chem. Lett. 1995; 5: 739-42) and J. Kobayashi et al. (Tetrahedron lett. 1988; 29: 1177-80) and on the model of human leukemia described by I. Bonnard et al. (Anti-cancer Drug design 1995; 10: 333-46). Several routes for synthesizing ascididemin have been reported by various authors: F. Bracher et al. (Heterocycles 1989; 29: 2093-95), C.J. Moody et al. (Tetrahedron Lett. 1992; 48: 3589-602) and G. Gellerman et al. (Synthesis 1994; 239-41).

Mention may also be made of 2-bromoleptoclinidone (according to the naming by S.J. Bloor et al. 1987) isolated from the ascidian *Leptoclinides sp.* by S.J. Bloor et al. (J. Ann. Chem. Soc. 1987; 109: 6134-6) and synthesized by F. Bracher et al. (Hétérocycles 1989; 29: 2093-95) and then by M.E. Jung et al. (Hétérocycles 1994; 39; 2: 767-778). 2-Bromoleptoclinidone shows cytotoxicity on the cellular model of leukemia with an ED_{50} of 0.4 μg/ml. The cytotoxic properties were confirmed by F. Bracher (Pharmazie 1997; 52: 57-60) both *in vitro* - on sixty tumor cell lines in culture - and *in vivo* on models of xenographs of human tumor cell lines (colon tumors SW-620 and HTC116, renal tumor A498 and melanoma LOX IM VI) implanted into mice.

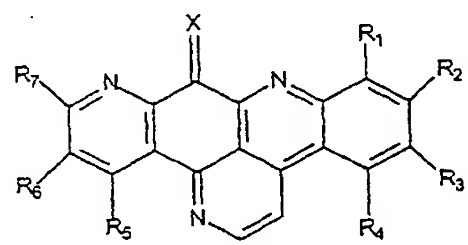
Other compounds derived from ascididemin, such as 11-hydroxy ascididemin, 11-methoxy ascididemin, 11-phenyl and 11-nitrophenyl ascididemin, 1-nitro and 3-nitro ascididemin and neocalliactin have been chemically described (according to the numbering by S.J. Bloor et al. 1987) by various teams such as those of F.J. Schmitz (J. Org. Chem. 1991; 56: 804-8) and Y. Kitahara et al. (Heterocycles 1993; 36: 943-46; Tetrahedron Lett. 1997; 53, 17029-38), G. Gellerman et

al. (Tetrahedron lett. 1993; 34: 1827-30), S. Nakahara et al (Heterocycles 1993; 36: 1139-44), I. Spector et al. (US Patent Number: 5,432,172, Jul. 11, 1995).

One subject of the present invention is a pharmaceutical composition comprising an effective amount of a compound chosen from the compounds of general formulae I and Ia below:



Formula I



Formula Ia

in which:

- X is chosen from oxygen, an =NH group and an =N-OH group,
- R_1 is chosen from hydrogen, halogens, a nitro group and groups $-NR_8R_9$ in which R_8 and R_9 are chosen, independently of each other, from hydrogen and (C_1-C_4) alkyl groups,
- R_2 is chosen from hydrogen and halogens,
- R_3 is chosen from hydrogen, halogens, (C_1-C_4) alkyl groups, (C_1-C_6) alkoxy groups, a guanidino group, groups $-NR_{10}R_{11}$ in which R_{10} and R_{11} are chosen, independently of each other, from hydrogen, (C_1-C_4) alkyl groups, (C_1-C_4) phenylalkyl groups and groups $-(CH_2)_n-Y$ with Y being chosen from halogens and CN, $-CH(O\text{-}Et)_2$, (C_1-C_6) alkoxy, $-O-(CH_2)_2-N(CH_3)_2$ and $-N(CH_3)_2$ groups and n = 1 to 3,
- R_4 is chosen from hydrogen, halogens, nitro groups and groups $-NR_{12}R_{13}$ in which R_{12} and R_{13} are chosen, independently of each other, from hydrogen and (C_1-C_4) alkyl groups,

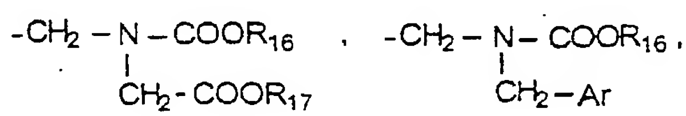
- R_5, R_6 and R_7 are chosen from:

hydrogen or a halogen atom,

C_1-C_6 alkyl, hydroxyl, C_1-C_6 alkoxy, $(C_1$-$C_6)$-alkoxy$(C_1$-$C_6)$alkyl, $(C_1$-$C_4)$alkylcarbonyloxy$(C_1$-$C_4)$alkyl, -CHO, -COOH, -CN, $-CO_2R_{14}$, $-CONHR_{14}$ and $-CONR_{14}R_{15}$ groups, $-NHCOR_{14}$ and $-NR_{14}R_{15}$ in which R_{14} and R_{15} are chosen, independently of each other, from hydrogen and $(C_1$-$C_6)$ alkyl, -phenyl-CO-CH_3 and $-CH_2-CH_2-N(CH_3)_2$ groups,

-phenyl-CO-CH_3 or -phenyl-CO-CH=CH-$N(CH_3)_2$, morpholino, nitro or SO_3H groups,

groups:



R_{16} and R_{17} being chosen from C_1-C_6 alkyl groups and Ar being a C_6-C_{14} aryl group,

with the exclusion of the compounds of formula I containing the combination:

X = O,

and, either: R_1, R_2, R_3, R_4, R_5, R_6, R_7 = H,

or : R_1, R_3, R_4, R_5, R_6, R_7 = H and R_2 = Br,

and with the exclusion of the compound formula Ia containing the combination X = O and R_1, R_2, R_3, R_4, R_5, R_6, R_7 = H,

and the addition salts of these compounds with pharmaceutically acceptable acids.

The present invention relates more particularly to a pharmaceutical composition comprising an effective amount of a compound chosen from the compounds of formula I in which:

- X is chosen from oxygen, an =NH group and an =N-OH group,

- R_1 is chosen from hydrogen, halogens, a nitro group and groups $-NR_8R_9$ in which R_8 and R_9 are chosen, independently of each other, from hydrogen and $(C_1$-$C_4)$ alkyl groups,

independently of each other, from hydrogen and (C_1-C_4) alkyl groups,

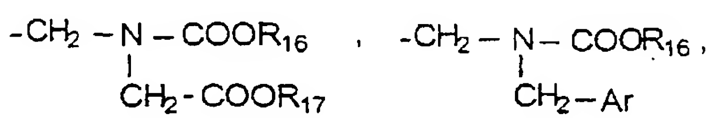
- R_2 is chosen from hydrogen and halogens,
- R_3 is chosen from hydrogen, halogens, (C_1-C_4) alkyl groups, (C_1-C_6) alkoxy groups, a guanidino group, groups $-NR_{10}R_{11}$ in which R_{10} and R_{11} are chosen, independently of each other, from hydrogen, (C_1-C_4) alkyl groups, (C_1-C_4) phenylalkyl, $-(CH_2)_2-N(CH_3)_2$, and $-(CH_2)_2-O-(CH_2)_2-N(CH_3)_2$ groups,
- R_4 is chosen from hydrogen, halogens, nitro groups and groups $-NR_{12}R_{13}$ in which R_{12} and R_{13} are chosen, independently of each other, from hydrogen and (C_1-C_4) alkyl groups,
- R_5, R_6 and R_7 are chosen from:

hydrogen or a halogen atom,

C_1-C_6 alkyl, hydroxyl, C_1-C_6 alkoxy, $-CHO$, $-COOH$, $-CN$, $-CO_2R_{14}$, $-CONHR_{14}$ and $-CONR_{14}R_{15}$ groups, $-NHCOR_{14}$ and $-NR_{14}R_{15}$ groups in which R_{14} and R_{15} are chosen, independently of each other, from hydrogen and (C_1-C_6) alkyl and $-CH_2-CH_2-N(CH_3)_2$ groups,

-phenyl-CO-CH_3 or -phenyl-CO-CH=CH-$N(CH_3)_2$, morpholino, nitro or SO_3H groups,

groups:



R_{16} and R_{17} being chosen from C_1-C_6 alkyl groups and Ar being a C_6-C_{14} aryl group,

with the exclusion of the compounds in which X = O, and, either : R_1, R_2, R_3, R_4, R_5, R_6, R_7 = H, or : R_1, R_3, R_4, R_5, R_6, R_7 = H and R_2 = Br,

and the addition salts of these compounds with pharmaceutically acceptable acids.

One subject of the present invention is more particularly a pharmaceutical composition comprising an

effective amount of a compound chosen from the compounds of formula I in which:

- X represents oxygen,
- R_1 is chosen from hydrogen and an amino group,
- R_2 is chosen from hydrogen and halogens,
- R_3 is chosen from hydrogen, halogens, (C_1-C_4) alkyl groups, (C_1-C_6) alkoxy groups, a guanidino group, groups $-NR_{10}R_{11}$ in which R_{10} and R_{11} are chosen, independently of each other, from hydrogen, methyl groups, (C_1-C_4) phenylalkyl, $-(CH_2)_2-N(CH_3)_2$, $(CH_2)_2-O-(CH_2)_2-N(CH_3)_2$ groups,
- R_4 is chosen from hydrogen, halogens and nitro and amino groups,
- R_5, R_6 and R_7 represent a hydrogen,

with the exclusion of the compounds in which R_1, R_2, R_3, R_4, R_5, R_6, R_7 = H, or R_1, R_3, R_4, R_5, R_6, R_7 = H and R_2 = Br,

and the addition salts of these compounds with pharmaceutically acceptable acids.

In its preferred form, one subject of the present invention is more particularly a pharmaceutical composition comprising an effective amount of a compound chosen from the compounds of formulae I and Ia in which:

- X represents oxygen,
- R_1 is chosen from hydrogen and an amino group,
- R_2 is chosen from hydrogen and halogens,
- R_3 is chosen from hydrogen, halogens, (C_1-C_4) alkyl groups, (C_1-C_6) alkoxy groups, a guanidino group, groups $-NR_{10}R_{11}$ in which R_{10} and R_{11} are chosen, independently of each other, from hydrogen, methyl groups, (C_1-C_4) phenylalkyl groups and groups $-(CH_2)_n-Y$ with Y being chosen from halogens and groups CN, $-CH(O-Et)_2$, (C_1-C_6) alkoxy, $-O-(CH_2)_2-N(CH_3)_2$ and $-N(CH_3)_2$ and n = 1 to 3,

- R_4 is chosen from hydrogen, halogens, and nitro and amino groups,
- R_5 is chosen from a hydrogen, a halogen and a methoxy group,
- R_6 and R_7 are chosen from hydrogen and C_1-C_6 alkoxy, (C_1-C_6)alkoxy(C_1-C_6)alkyl and $-CH_2OCOCH_3$ groups,

with the exclusion of the compounds of formula I in which R_1, R_2, R_3, R_4, R_5, R_6, R_7 = H or R_1, R_3, R_4, R_5, R_6, R_7 = H and R_2 = Br, and of the compound of formula Ia in which R_1, R_2, R_3, R_4, R_5, R_6, R_7 = H,

and the addition salts of these compounds with pharmaceutically acceptable acids.

A subject of the present invention is also the compounds of formula I as defined above, with the exclusion of the compounds in which X = O, and

either R_1, R_2, R_3, R_4, R_5, R_6, R_7 = H,
or R_1, R_3, R_4, R_5, R_6, R_7 = H and R_2 = Br,
or R_1, R_2, R_4, R_5, R_6, R_7 = H and R_3 = OCH_3,
or R_1, R_2, R_3, R_4, R_6, R_7 = H and R_5 = OH or OCH_3,
or R_1 = NO_2 and R_2, R_3, R_4, R_6, R_7 = H,

and the addition salts of these compounds with pharmaceutically acceptable acids.

A subject of the present invention is also the compounds of formula Ia as defined above, with the exclusion of the compound in which X = O and R_1, R_2, R_3, R_4, R_5, R_6, R_7 = H,

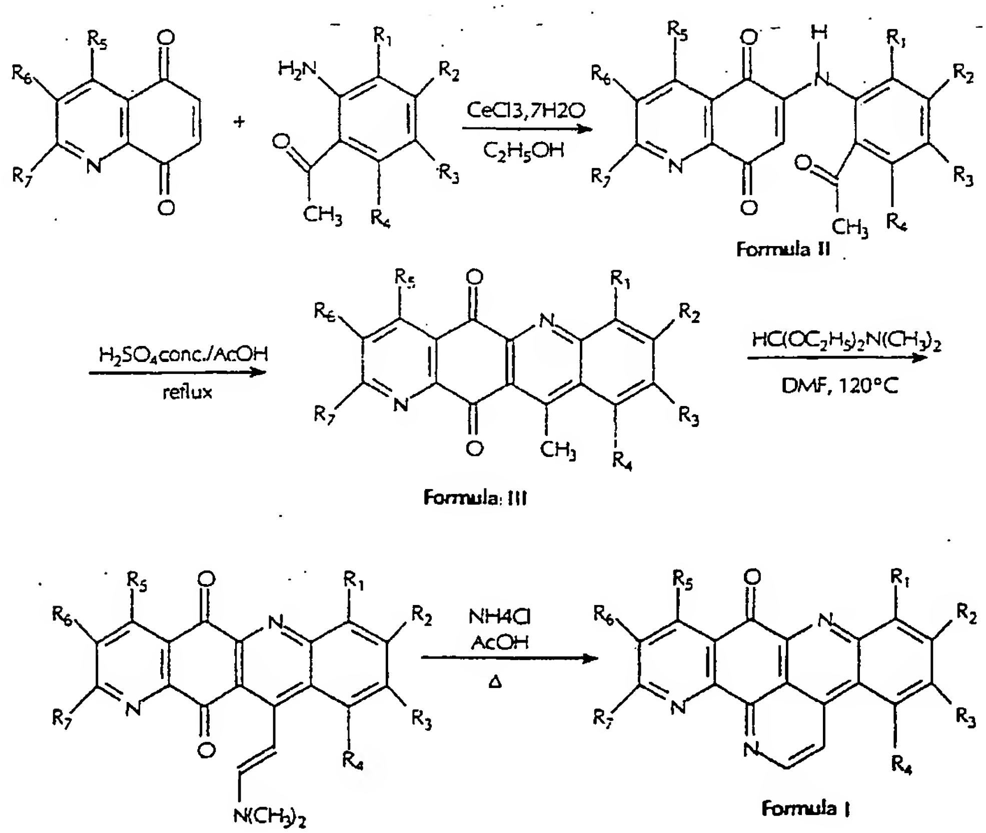
and the addition salts of these compounds with pharmaceutically acceptable acids.

The expression "addition salts with pharmaceutically acceptable acids" denotes salts which give the biological properties of the free bases, without having any adverse effects. These salts may be especially those formed with mineral acids, such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid or phosphoric acid; acidic metal salts, such as disodium

orthophosphate and monopotassium sulfate, and organic acids.

In general, the compounds of formula I are obtained according to the general reaction scheme described by F. Bracher *et al.* (Heterocycles 1989; 29: 2093-95) for ascididemin. According to this scheme, the compounds are prepared by oxidative amination of a 5,8-quinone substituted with a substituted ortho-aminoacetophenone, followed by cyclization of the diarylamine obtained (compounds of the formula II) into an intermediate tetracyclic quinone (compounds of formula III). The enamine formed by reaction of the compound of formula III with dimethylformamide diethyl acetal gives the final derivative by cyclization:

Scheme I



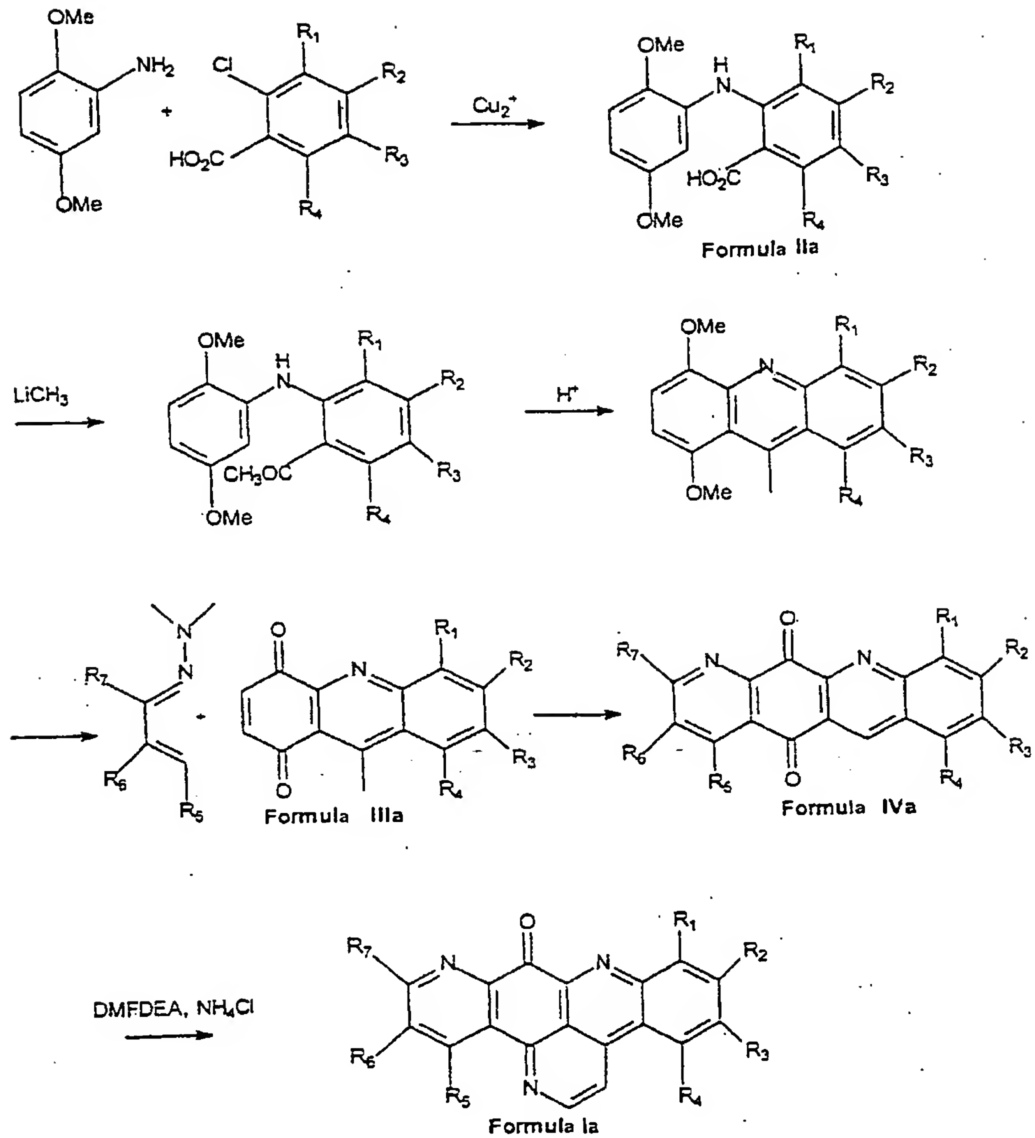
Ascididemin (or 9-*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one) was prepared according to the process described by F. Bracher *et al.* (Heterocycles 1989; 29: 2093-95) and is referenced, in the present document, under the number CRL 8274.

Certain compounds may be prepared directly from ascididemin or from a compound of formula I used as a synthetic intermediate.

Thus, in particular, the compounds of formula I in which R_3 is a group $-NR_{10}R_{11}$, where R_{10} and/or R_{11} are other than hydrogen, may be obtained from a compound of formula I in which R_3 is an $-NH_2$ group.

Similarly, the compounds of formula Ia may be obtained according to the general reaction scheme II. According to this scheme, the compounds are prepared by coupling a substituted chlorobenzoic acid and dimethoxyaniline to form the compounds of formula IIa. After conversion of the acid function to a methyl ketone, cyclization and then oxidation, an intermediate tricyclic quinone (compound of formula IIIa) is obtained. A Diels-Alder cycloaddition with a 1-azediene leads to the formation of a tetracyclic quinone (compound of formula IVa). The addition of dimethylformamide diethyl acetal to this quinone gives an enamine intermediate which is cyclized, in the presence of ammonium chloride, to the final compound of formula Ia.

Scheme II


OMe
NH2
Cl
R1
R2
R3
R4
HO2C
Cu2+
H
N
Formula IIa
LiCH3
CH3OC
H+
N
O
R5
R6
R7
Formula IIIa
Formula IVa
DMFDEA, NH4Cl
Formula Ia

Certain compounds may be prepared directly from the ascididemin isomer known as 9-*H*-quino[4,3,2-*de*]-[1,7]phenanthrolin-9-one, or from a compound of formula Ia used as a synthetic intermediate.

Certain compounds may be prepared directly from the ascididemin isomer known as 9-*H*-quino[4,3,2-*de*]-[1,7]phenanthrolin-9-one, or from a compound of formula Ia used as a synthetic intermediate.

Thus, in particular, the compounds of formula Ia in which R_3 is a group $-NR_{10}R_{11}$, in which R_{10} and/or R_{11} are other than hydrogen, may be obtained from a compound of formula Ia in which R_3 is a $-NH_2$ group.

A - Preparation of the intermediate products of formula II (Scheme I)

A-1 - Synthesis of 6-(2-acetyl-4-methylphenylamino)-quinoline-5,8-dione (Intermediate A_1) (CRL 8322)

A solution of 5,8-quinolinedione (0.215 g, 1.35 mmol) in 12 ml of ethanol is added slowly to a solution of cerium chloride (1 g, 2.7 mmol) and 5-methyl-2-amino-acetophenone (0.402 g, 2.7 mmol) in 5 ml of ethanol. The reaction medium (red) is stirred overnight at room temperature. The resulting medium is hydrolyzed with 30 ml of aqueous 10% acetic acid solution and extracted 4 times with chloroform. The organic phases are dried over $MgSO_4$ and then evaporated. The crude product obtained is purified by flash chromatography on a column of silica (95/5 CH_2Cl_2/MeOH) to give 0.405 g of the expected tricyclic compound in the form of a powder:

- Yield = 98%
- ^1H NMR ($CDCl_3$): 2.42 (s, 3H), 2.77 (s, 3H), 6.86 (s, 1H), 7.38 (dd, 1H, J = 8 and 1.6 Hz), 7.52 (d, 1H, J = 8 Hz), 7.61 (dd, 1H, J = 5.2 and 7.6 Hz), 7.74 (d,

1H, J = 1.6 Hz), 8.46 (dd, 1H, J = 7.6 and 5.2 Hz), 9.02 (dd, 1H, J = 2 and 5.2 Hz), 11.18 (s, 1H).

A-2 - Synthesis of 6-(2-acetyl-4-chlorophenylamino)quinoline-5,8-dione (Intermediate A_2)

Preparation according to the process described in chapter A-1: quinoline-5,8-dione (0.188 g, 1.18 mmol), cerium chloride (0.88 g, 2.36 mmol), 5-chloro-2-aminoacetophenone (0.4 g, 3.14 mmol), ethanol (10 + 4 ml), acetic acid (25 ml). 0.3 g of a red powder is obtained:

- Yield = 78%
- ^{1}H NMR ($CDCl_3$): 2.65 (s, 3H), 6.84 (s, 1H), 7.52 (dd, 1H, J = 8.8 Hz), 7.57 (d, 1H, J = 8.8 Hz), 7.63 (dd, 1H, J = 8 and 4.4 Hz), 7.89 (d, 1H, J = 2.4 Hz), 8.46 (dd, 1H, J = 0.8 and 8 Hz), 9.02 (dd, 1H, J = 2 and 5.2 Hz), 11.18 (s, 1H).
- ^{13}C NMR ($CDCl_3$): 28.5; 107.36; 121.86; 126.69; 126.85; 127.49; 128.39; 132.10; 134.06; 134.75; 138.36; 143.29; 148.32; 155.22; 181.28; 182.63; 200.39.

A-3 - Synthesis of 6-(2-acetyl-4-benzylaminophenylamino)quinoline-5,8-dione (Intermediate A_3)

Preparation according to the process described in chapter A-1: quinoline-5,8-dione (0.250 g, 1.57 mmol), cerium chloride (0.77 g, 3.14 mmol), 5-benzylamino-2-aminoacetophenone (0.603 g, 3.14 mmol), ethanol (15 + 7 ml), acetic acid (35 ml). 0.56 g of a red powder is obtained:

- Yield = 91%
- ^{1}H NMR ($CDCl_3$): 2.54 (s, 3H), 4.38 (s, 2H), 6.70 (s, 1H), 6.83 (dd, 1H, J = 9.6 and 3.2 Hz), 7.08 (d, 1H, J = 3.2 Hz), 7.30-7.37 (m, 5H), 7.43 (d, 1H, J = 9.6 Hz), 7.58 (dd, 1H, J = 7.6 and 4.8 Hz), 8.43 (dd, 1H, J = 7.6 and 2 Hz), 9.03 (dd, 1H, J = 2 and 4.8 Hz), 10.67 (s, 1H).

A-4 - Synthesis of 6-(2-acetyl-5-bromophenylamino)quinoline-5,8-dione (Intermediate A_4) (CRL 8268)

Preparation according to the process described by F. Bracher, Liebigs Ann. Chem. 1990, 205-206.

A-5 - Synthesis of 6-(2-acetyl-4-dimethylaminophenylamino)quinoline-5,8-dione (Intermediate A_5)

Preparation according to the process described in chapter A-1: quinoline-5,8-dione (0.36 g, 2.26 mmol), cerium chloride (1.67 g, 4.49 mmol), 5-dimethylamino-2-aminoacetophenone (0.8 g, 4.49 mmol), ethanol (20 + 10 ml), acetic acid (50 ml). 1.26 g of a red powder are obtained:

- Yield = 84%
- ^1H NMR ($CDCl_3$): 2.85 (s, 3H), 3.12 (s, 6H), 6.72 (s, 1H), 6.90 (dd, 1H, J = 2.8 and 9.2 Hz), 7.15 (d, 1H, J = 2.8 Hz), 7.49 (d, 1H, J = 9.2 Hz), 7.58 (dd, 1H, J = 8 Hz and 4.4 Hz), 8.43 (dd, 1H, J = 1.6 and 8 Hz), 9.00 (dd, 1H, J = 1.6 and 4.4 Hz), 10.69 (s, 1H).

A-6 - Synthesis of 6-(2-acetyl-4-methoxyphenylamino)quinoline-5,8-dione (Intermediate A_6)

Preparation according to the process described in chapter A-1: quinoline-5,8-dione (3.51 g, 22.08 mmol), cerium chloride (16.4 g, 44.03 mmol), 5-methoxy-2-aminoacetophenone (7.29 g, 44.18 mmol), ethanol (200 + 90 ml), acetic acid (500 ml). 4.25 g of a red powder are obtained:

- Yield = 60%
- ^1H NMR ($CDCl_3$): 2.65 (s, 3H), 3.87 (s, 3H), 6.76 (s, 1H), 7.12 (dd, 1H, J = 2.8 and 8.8 Hz), 7.42 (d, 1H, J = 2.8 Hz), 7.55 (d, 1H, J = 8.8 Hz), 7.61 (dd, 1H, J = 7.6 and 4.4 Hz), 8.45 (dd, 1H, J = 1.6 and 7.6 Hz), 9.01 (dd, 1H, J = 1.6 and 4.4 Hz), 10.80 (s, 1H).

A-7 - Synthesis of 4,6-bis(2-acetylanilino)quinoline-5,8-dione (Intermediate A_7)

Preparation according to the process described in chapter A-1: 4-chloroquinoline-5,8-dione (3.5 g, 18 mmol), cerium chloride (13.5 g, 36.24 mmol), 2-aminoacetophenone (4.4 ml, 36 mmol), ethanol (160 + 70 ml), acetic acid (400 ml). 2.32 g of a red powder are obtained:

- Yield = 30%
- ^1H NMR ($CDCl_3$): 2.69 (s, 3H), 2.72 (s, 3H), 6.85 (s, 1H), 7.18 (ddd, 1H, J = 7.6 and 7.6 and 0.8 Hz), 7.28 (m, 1H), 7.30 (d, 1H, J = 6.4 Hz), 7.54-7.59 (m, 3H), 7.63 (d, 1H, J = 7.6 Hz), 7.91 (dd, 1H, J = 1.6 and 8.4 Hz), 7.94 (dd, 1H, J = 1.2 and 8.4 Hz), 8.47 (d, 1H, J = 6.4 Hz), 11.35 (s, 1H), 12.35 (s, 1H).

A-8 - Synthesis of 6-(2-acetyl-4-bromophenylamino)-4-methoxyquinoline-5,8-dione (Intermediate A_8)

Preparation according to the process described in chapter A-1: 4-methoxyquinoline-5,8-dione (1.57 g, 9.1 mmol), cerium chloride (3.1 g, 8.3 mmol), 5-bromo-2-aminoacetophenone (Leonard, Boyd, J. Org. Chem. 1946; 11, 419-423) (1.95 g, 9.1 mmol), ethanol (200 ml), acetic acid (180 ml). After purification by flash chromatography on a column of silica (95/5 CH_2Cl_2/MeOH), 1.22 g of an orange powder are obtained:

- Yield = 37%
- ^1H NMR ($CDCl_3$): 3.15 (s, 3H), 4.58 (s, 3H), 7.61 (d, 1H, J = 6 Hz), 7.74 (s, 1H), 7.99 (d, 1H, J = 8.8 Hz), 8.14 (dd, 1H, J = 8.8 and 2.4 Hz), 8.51 (d, 1H, J = 2.8 Hz), 9.32 (d, 1H, J = 6 Hz), 11.68 (s, 1H).

A-9 - Synthesis of 2-methoxy-6-(2-acetylphenylamino)quinoline-5,8-dione (Intermediate A_9)

A solution of o-aminoacetophenone (0.41 g, 3.1 mmol) in ethanol (6 ml) is added to a suspension of 2-methoxy-quinoline-5,8-dione (0.54 g, 2.8 mmol) and cerium

chloride (1.16 g, 4.7 mmol) in ethanol (100 ml). The reaction medium is stirred at room temperature for 40 hours. After concentration on a rotary evaporator, the crude product obtained is purified by filtration on silica (98/2 $CHCl_3$/heptane) to give the expected codensation product in the form of a red powder (0.35 g).

- Yield = 38%
- Melting point = 258°C
- ^{1}H NMR ($CDCl_3$): 2.67 (s, 3H), 4.15 (s, 3H), 6.79 (s, 1H), 6.98 (d, 1H, J = 8.8 Hz), 7.18 (ddd, 1H, J = 8.1, 8.4 and 1.5 Hz), 7.56 (dd, 1H, J = 8.4 and 1.5 Hz), 7.61 (ddd, 1H, J = 8.1 and 8.4 and 1.1 Hz), 7.94 (dd, 1H, J = 8.1 and 1.5 Hz), 8.31 (d, 1H, J = 8.8 Hz).
- ^{13}C NMR ($CDCl_3$): 28.51, 54.73, 106.02, 115.22, 120.78, 122.50, 123.11, 125.70, 132.34, 134.24, 137.18, 140.05, 143.30, 148.21, 167.75, 180.88, 183.05, 201.41.
- IR ($CHCl_3$): 1668, 1644 cm^{-1}.

A-10 - Synthesis of 3-hydroxymethyl-6-(2-acetylphenylamino)quinoline-5,8-dione (Intermediate A_{10})

a) - 3-Hydroxymethyl-5,8-dimethoxyquinoline

A solution of 1M $LiAlH_4/Et_2O$ (5 ml, 5 mmol) is added dropwise and under nitrogen to a solution of ethyl 5,8-dimethoxyquinoline-3-carboxylate (180 mg, 0.689 mmol) in 60 ml of THF. The mixture is stirred at room temperature for 15 hours and then poured into 15 ml of 1N NaOH and 40 ml of water. After extraction with CH_2Cl_2 (3 × 100 ml) and then drying of the organic phase over $MgSO_4$, the extract is concentrated on a rotary evaporator. The crude product obtained is purified by flash chromatography (95/5 CH_2Cl_2/MeOH) to give the expected product in the form of a brown powder (72 mg):

- Yield = 48%
- Melting point = 150°C

- ^1H NMR ($CDCl_3$): 3.92 (s, 3H), 4.00 (s, 3H), 4.88 (s, 2H), 6.72 (d, 1H, J = 8.4 Hz), 6.88 (d, 1H, J = 8.4 Hz), 8.47 (d, 1H, J = 2.2 Hz), 8.87 (d, 1H, J = 2.2 Hz)
- ^{13}C NMR ($CDCl_3$): 55.76, 56.00, 63.09, 103.95, 106.70, 121.25, 128.62, 133.35, 139.80, 148.61, 149.21, 149.41.
- IR ($CDCl_3$): 3607, 3417, 1622, 1605 cm^{-1}.

b) – 3-Hydroxymethylquinoline-5,8-dione

A solution of 3-hydroxymethyl-5,8-dimethoxyquinoline (55 mg, 0.25 mmol) and cerium ammonium nitrate (550 mg, 1 mmol) in a CH_3CN/H_2O mixture (3 ml/1 ml) is stirred at room temperature for 40 minutes. After addition of 5 ml of H_2O and 10 ml of saturated $NaHCO_3$ solution, the medium is extracted with CH_2Cl_2 (6 × 30 ml) and the organic phases are dried over $MgSO_3$. After evaporating off the solvent on a rotary evaporator, the expected quinone is obtained in the form of a brown powder (11 mg):

- Yield = 22%
- Melting point = 150°C
- ^1H NMR ($CDCl_3$): 4.95 (s, 2H), 7.06 (d, 1H, J = 10.2 Hz), 7.15 (d, 1H, J = 10.2 Hz), 8.43 (s, 1H), 9.03 (s, 1H).
- ^{13}C NMR ($CDCl_3$): 62.03, 128.86, 132.26, 138.00, 139.11, 141.33, 146.58, 153.10, 183.12, 184.54.
- IR ($CHCl_3$): 3413, 1680, 1596 cm^{-1}.

c) – Synthesis of 3-hydroxymethyl-6-(2-acetylphenylamino)quinoline-5,8-dione (Intermediate A_{10})

A solution of 2-aminoacetophenone (0.18 g, 1.33 mmol) is added to a suspension of 3-hydroxymethylquinoline-5,8-dione (0.22 g, 1.16 mmol) and cerium chloride (0.6 g, 2.43 mmol) in ethanol (40 ml). The reaction medium is stirred at room temperature in darkness for 3 hours. After concentrating on a rotary evaporator, the crude product obtained is purified by filtration on silica (98/2 CH_2Cl_2/MeOH) to give the expected

condensation product in the form of a violet powder (0.16 g):

- Yield = 42%
- Melting point = 258°C
- ^1H NMR (DMSO-d_6): 2.67 (s, 3H), 4.73 (d, 2H, J = 5.5 Hz), 5.67 (t, 1H, J = 5.5 Hz), 6.64 (s, 1H), 7.30 (m, 1H), 7.71 (m, 2H), 8.12 (d, 1H, J = 8.0 Hz), 8.35 (d, 1H, J = 2.0 Hz), 8.93 (d, 1H, J = 2.0 Hz), 11.02 (s, 1H).
- ^{13}C NMR ($CDCl_3$): 28.81, 60.08, 106.52, 120.96, 123.44, 126.14, 127.23, 131.52, 132.69, 134.43, 138.91 141.75, 143.55, 146.62, 152.81, 181.62, 181.84, 202.02.
- IR ($CHCl_3$): 3440, 1690, 1661, 1640 cm^{-1}.

B - Preparation of the intermediate products of formula III (Scheme II)

B-1 - Synthesis of 9,11-dimethyl-1,6-diazanaphthacene-5,12-dione (Intermediate B_1) (CRL 8324)

1.9 ml of sulfuric acid dissolved in 9.6 ml of acetic acid are added slowly to a solution of tricyclic intermediate A_1 (0.4 g, 1.3 mmol) in 12 ml of acetic acid. The reaction medium is refluxed for 30 minutes and, after cooling, is then poured into a beaker containing crushed ice. The mixture is neutralized with NH_4OH and then extracted 4 times with dichloromethane. The organic phases are dried over $MgSO_4$ and then evaporated. The crude product obtained is purified by flash chromatography on a column of silica (95/5 CH_2Cl_2/MeOH) to give 0.325 g of the expected tetracyclic compound.

- Yield = 86%
- ^1H NMR ($CDCl_3$): 2.64 (s, 3H), 3.29 (s, 3H), 7.74 (dd, 1H, J = 7.6 and 4.8 Hz), 7.75 (dd, 1H, J = 8.4 and 1.6 Hz), 8.12 (dd, J = 1.6 Hz), 8.33 (d, 1H, J = 8.4), 8.71 (dd, 1H, J = 2 and 7.6 Hz), 9.13 (dd, 1H, J = 2 and 4.8 Hz).

B-2 - Synthesis of 9-chloro-11-methyl-1,6-diazanaphthacene-5,12-dione (Intermediate B_2)

Preparation according to the process described in chapter B-1: tricyclic intermediate A_2 (0.289 g, 0.88 mmol), sulfuric acid (1.3 ml), acetic acid (8 + 6.5 ml). After purification by flash chromatography (95/5 CH_2Cl_2/MeOH), 0.26 g of tetracycle is obtained:

- Yield = 95%
- ^1H NMR ($CDCl_3$): 3.25 (s, 3H), 7.76 (dd, 1H, J = 8 and 4.8 Hz), 7.85 (dd, 1H, J = 8.8 and 2 Hz), 8.33 (dd, 1H, J = 2 Hz), 8.38 (d, 1H, J = 8.8), 8.71 (dd, 1H, J = 1.6 and 8 Hz), 9.15 (dd, 1H, J = 1.6 and 4.8 Hz).

B-3 - Synthesis of 9-benzylamino-11-methyl-1,6-diazanaphthacene-5,12-dione (Intermediate B_3)

Preparation according to the process described in chapter B-1: tricyclic intermediate A_3 (4 g, 10 mmol), sulfuric acid (15.1 ml), acetic acid (92 + 75 ml). After work-up, 3.58 g of tetracycle are obtained.

- Yield = 98%
- ^1H NMR ($CDCl_3$): 3.09 (s, 3H), 4.52 (d, 2H), 4.86 (t, 1H), 7.06 (d, 1H, J = 2.8 Hz), 7.29 (dd, 1H, J = 9.2 and 2.8 Hz), 7.3-7.43 (m, 5H), 7.71 (dd, 1H, J = 4.8 and 8 Hz), 8.20 (d, 1H, J = 9.8 Hz), 8.69 (dd, 1H, J = 1.6 and 8 Hz), 9.09 (dd, 1H, J = 1.6 and 4.8 Hz).

B-4 - Synthesis of 8-bromo-11-methyl-1,6-diazanaphthacene-5,12-dione (Intermediate B_4)

Preparation according to the process described by F. Bracher, Liebigs Ann. Chem. 1990, 205-206.

B-5 - Synthesis of 9-dimethylamino-11-methyl-1,6-diazanaphthacene-5,12-dione (Intermediate B_5)

Preparation according to the process described in chapter B-1: intermediate tricycle A_5 (0.76 g, 2.27 mmol), sulfuric acid (3.5 ml), acetic acid (20 + 18 ml). After work-up, 0.67 g of tetracycle is obtained.

- Yield = 93%
- ^{1}H NMR ($CDCl_3$): 3.17 (s, 3H), 3.21 (s, 6H), 7.04 (d, 1H, J = 3.2 Hz), 7.51 (dd, 1H, J = 3.2 and 9.2 Hz), 7.71 (dd, 1H, J = 8 and 4.4 Hz), 8.26 (d, 1H, J = 9.2 Hz), 8.7 (dd, 1H, J = 1.6 and 8 Hz) 9.09 (dd, 1H, J = 1.6 and 4.4 Hz).

B-6 - Synthesis of 9-methoxy-11-methyl-1,6-diazanaphthacene-5,12-dione (Intermediate B_6)

Preparation according to the process described in chapter B-1: intermediate tricycle A_6 (4.25 g, 13.18 mmol), sulfuric acid (20 ml), acetic acid (110 + 100 ml). The product obtained by flash chromatography (100/3 CH_2Cl_2/MeOH) is washed with ethyl ether to give 2.9 g of tetracycle.

- Yield = 72%
- ^{1}H NMR ($CDCl_3$): 3.25 (s, 3H), 4.02 (s, 3H), 7.49 (d, 1H, J = 3.3 Hz), 7.56 (dd, 1H, J = 3.3 and 9.3 Hz), 7.74 (dd, 1H, J = 8.3 and 4.3 Hz), 8.34 (d, 1H, J = 9.3 Hz), 8.71 (dd, 1H, J = 2.5 and 8.3 Hz), 9.12 (dd, 1H, J = 2.5 and 4.3 Hz).

B-7 - Synthesis of 4-(2-acetylanilino)-11-methyl-1,6-diazanaphthacene-5,12-dione (Intermediate B_7) (CRL 8332)

Preparation according to the process described in chapter B-1: intermediate tricycle A_7 (1 g, 2.35 mmol), sulfuric acid (3.5 ml), acetic acid (18 ml). The product obtained by flash chromatography (100/3 CH_2Cl_2/MeOH) is washed with ethyl ether to give 0.6 g of tetracycle in the form of an orange powder.

- Yield = 63%
- ^{1}H NMR ($CDCl_3$): 2.59 (s, 3H), 3.25 (s, 3H), 7.29 (ddd, 1H, J = 7.2 and 7.2 and 1.2 Hz), 7.37 (d, 1H, J = 6 Hz), 7.54 (ddd, 1H, J = 6.8 and 6.8 and 1.6 Hz), 7.59 (d, 1H, J = 6.8 Hz), 7.74 (dd, 1H, J = 7.2 and 1.2 Hz), 7.76 (dd, 1H, J = 6.8 and 1.6 Hz), 7.87-7.918 (m, 2H), 8.34 (d, 1H, J = 8.4 Hz), 8.43 (d, 1H, J = 8.4 Hz), 8.54 (d, 1H, 6 Hz), 12.5 (s, 1H).

B-8 – Synthesis of 4-methoxy-9-bromo-11-methyl-1,6-diazanaphthacene-5,12-dione (Intermediate B_8)

Preparation according to the process described in chapter B-1: intermediate tricycle A_8 (1.22 g, 3.04 mmol), sulfuric acid (4.5 ml), acetic acid (27 + 23 ml). The product obtained by flash chromatography (100/3 CH_2Cl_2/MeOH) is washed with ethyl ether to give 0.76 g of tetracycle in the form of a yellow powder.

- Yield = 65%
- ^1H NMR ($CDCl_3$): 3.21 (s, 3H), 4.10 (s, 3H), 7.18 (d, 1H, J = 6 Hz), 7.96 (dd, 1H, J = 8.8 and 2 Hz), 8.27 (d, 1H, J = 8.8 Hz), 8.47 (d, 1H, J = 2 Hz), 8.89 (d, 1H, J = 6 Hz).

B-9 – Synthesis of 2-methoxy-11-methyl-1,6-diazanaphthacene-5,12-dione (Intermediate B_9)

A solution of 2-methoxy-6-(2-acetylphenylamino)quinoline-5,8-dione (0.34 g, 1.1 mmol) in an acetic acid/sulfuric acid mixture (25 mol/2.7 ml) is heated at 90°C for 45 minutes. After cooling, the reaction medium is poured into a water/ice mixture (200 ml) and then basified to pH 8 with K_2CO_3 and extracted with $CHCl_3$ (3 × 200 ml). The organic phases are dried over $MgSO_4$ and then concentrated on a rotary evaporator. The crude product obtained is purified by filtration on silica ($CHCl_3$) to give the expected tetracycle in the form of a beige-colored powder (0.23 g):

- Yield = 71%
- Melting point = 260°C
- ^1H NMR ($CDCl_3$): 3.32 (s, 3H), 4.23 (s, 3H), 7.14 (d, 1H, J = 8.8 Hz), 7.79 (ddd, 1H, J = 8.6, 8.4 and 1.2 Hz), 7.91 (ddd, 1H, J = 8.4, 8.6 and 1.2 Hz), 8.38 (dd, 1H, J = 8.6 and 1.2 Hz), 8.46 (dd, 1H, J = 8.4 and 1.2 Hz), 8.58 (d, 1H, J = 8.8 Hz).
- ^{13}C NMR ($CDCl_3$): 16.63, 54.76, 117.29, 125.29, 125.50, 125.64, 129.62, 129.75, 132.37, 132.57, 138.12, 147.73, 148.63, 149.69, 152.28, 167.77, 181.10, 183.55.

- IR ($CHCl_3$): 1683, 1599 cm^{-1}

B-10 – Synthesis of 3-acetoxymethyl-11-methyl-1,6-diazanaphthacene-5,12-dione (Intermediate B_{10})

A solution of 3-hydroxymethyl-6-(2-acetylphenylamino)-quinoline-5,8-dione (*Intermediate A_{10}*), (0.248 g, 0.77 mmol) in an acetic acid/sulfuric acid mixture (16 ml/1.3 ml) is heated at 90°C for 2 hours 30 minutes. After cooling, the reaction medium is poured into a water/ice mixture (15 ml) and then basified to pH 9 with Na_2CO_3. The medium is then extracted with CH_2Cl_2 (3 × 150 ml). The organic phases are dried over $MgSO_4$ and then concentrated on a rotary evaporator. The crude product obtained is purified by filtration through silica (98/2 CH_2Cl_2/MeOH) to give the expected compound in the form of a brown powder (0.21 g).

- Yield = 85%
- Melting point = 210°C
- ^1H NMR ($CDCl_3$): 2.18 (s, 3H), 3.30 (s, 3H), 5.31 (s, 2H), 7.78 (ddd, 1H, J = 1.1, 6.8 and 8.1 Hz), 7.92 (ddd, 1H, J = 1.1, 6.8 and 8.1 Hz), 8.37 (dd, 1H, J = 8.1 and 1.1 Hz), 8.43 (dd, 1H, J = 8.1 and 1.1 Hz), 8.66 (d, 1H, J = 2.2 Hz), 9.09 (d, 1H, J = 2.2 Hz).
- ^{13}C NMR ($CDCl_3$): 16.06, 20.11, 62.06, 124.81, 124.91, 129.06, 129.18, 129.29, 131.70, 132.18, 134.06, 136.09, 146.86, 147.97, 149.01, 152.19, 154.30, 169.72, 180.96, 182.34.
- IR ($CHCl_3$): 3420, 1746, 1692 cm^{-1}

C – Preparation of the intermediate products of formula IIIa (Scheme II)

1) Synthesis of N-(2,5-dimethoxyphenyl)anthranilic acid (Compound 4)

A mixture of 2-chlorobenzoic acid (9.2 g, 60 mmol), dimethoxyaniline (10 g, 65 mmol), copper (0.96 g), Cu_2O (0.96 g) and K_2CO_3 (10.4 g) in 120 ml of diglyme is

refluxed overnight. After evaporating off the solvent, the reaction medium is basified with 1N sodium hydroxide. Ether is added and the medium is then filtered through silica and the ether phase is removed. The aqueous phase is acidified with concentrated HCl and then extracted with ethyl acetate. After drying over $MgSO_4$ and evaporating off the solvent on a rotary evaporator, the crude product obtained is purified by filtration through silica (CH_2Cl_2) to give the expected condensation product in the form of a yellow powder (14.5 g).

- Yield = 89%
- Melting point = 138°C
- ^1H NMR ($CDCl_3$): 3.77 (s, 3H), 3.85 (s, 3H), 6.57 (dd, 1H, J = 8.8 and 2.9 Hz), 6.77 (ddd, 1H, J = 1.9 and 7.5 Hz), 6.87 (d, 1H, J = 9.2 Hz), 7.04 (d, 1H, J = 2.9 Hz), 7.3 to 7.4 (m, 2H), 9.35 (broad s, 1H)
- ^{13}C NMR ($CDCl_3$): 55.76, 56.45, 107.30, 107.71, 112.00, 112.26, 114.70, 117.53, 130.78, 132.60, 134.09, 145.98, 147.71, 153.75, 172.95
- IR ($CHCl_3$): 3327, 1685 cm^{-1}

2) Synthesis of 2-(2,5-dimethoxyphenylamino)acetophenone (Compound 5)

16 ml of MeLi (1.4 M/Et_2O) are added at 0°C and under N_2 to a mixture of N-(2,5-dimethoxyphenyl)anthranilic acid (2 g, 73 mmol) in 14 ml of THF. After raising the temperature, the medium is refluxed for 2 hours, 100 ml of water are then added and the mixture is extracted with ether (3 × 100 ml). After drying over $MgSO_4$, the solvent is evaporated off on a rotary evaporator to give the expected derivative in the form of a yellow solid (1.49 g).

- Yield = 75%
- Melting point = 79°C
- ^1H NMR ($CDCl_3$): 2.64 (s, 3H), 3.76 (s, 3H), 3.84 (s, 3H), 6.55 (dd, 1H, J = 8.8 and 2.9 Hz), 6.73 (dd, 1H, J = 1.4 and 7.5 Hz), 6.85 (d, 1H, J = 8.8 Hz), 7.04

(d, 1H, J = 2.9 Hz), 7.3 to 7.4 (m, 2H), 7.81 (dd, 1H, J = 1.5 and 8.0 Hz), 10.5 (broad s, 1H).

- ^{13}C NMR ($CDCl_3$): 48.15, 55.73, 56.36, 107.10, 107.72, 112.05, 114.80, 116.84, 120.09, 130.68, 132.42, 134.35, 145.98, 146.67, 153.62, 201.00
- IR ($CHCl_3$): 3350, 1642 cm^{-1}

3) Synthesis of 1,4-dimethoxy-9-methylacridine (Compound 6)

A mixture of 2-(2,5-dimethoxyphenylamino)acetophenone (1.3 g, 48 mmol) and polyphosphoric acid (13 g, 133 mmol) is heated at 100°C for 1 hour. After addition of 50 ml of water, the mixture is neutralized with 4M sodium hydroxide and then extracted with $CHCl_3$ (3 x 100 ml). After drying over $MgSO_4$ and evaporating off the solvent, the crude product obtained is purified by filtration through silica (CH_2Cl_2) to give the expected tricyclic derivative quantitatively in the form of a brown-orange solid.

- Melting point = 136°C
- ^{1}H NMR ($CDCl_3$): 3.36 (s, 3H), 3.96 (s, 3H), 4.09 (s, 3H), 6.68 (d, 1H, J = 8.0 Hz), 6.89 (d, 1H, J = 8.4 Hz), 7.54 (m, 1H), 7.73 (m, 1H), 8.32 (d, 1H, J = 8.4), 8.36 (d, 1H, J = 8.8 Hz)
- ^{13}C NMR ($CDCl_3$): 17.78, 55.66, 56.13, 102.43, 105.18, 120.25, 124.28, 125.62, 126.59, 129.44, 130.81, 142.45, 144.23, 147.21, 149.46, 151.45
- IR ($CHCl_3$): 1685, 1661 cm^{-1}

4) Synthesis of 9-methylacridine-1,4-dione (Compound 7)

A solution of 1,4-dimethoxy-9-methylacridine (20 mg, 0.079 mmol) and cerium ammonium nitrate (196 mg, 0.357 mmol) in a CH_2Cl_2/H_2O mixture (0.5 ml/0.25 ml) is stirred at 0°C for 20 minutes. After adding 1.4 ml of H_2O and 0.4 ml of saturated $NaHCO_3$ solution, the medium is left stirring and is then extracted with CH_2Cl_2 (3 x 3 ml). The organic phases are dried over $MgSO_4$. After evaporating off the solvent on a rotary

evaporator, the expected quinone is obtained in the form of a brown powder (15 mg).

- Yield = 90%
- Melting point = > 260°C
- ^{1}H NMR ($CDCl_3$): 3.22 (s, 3H), 7.09 (d, 1H, J = 10.3 Hz), 7.18 (d, 1H, J = 10.3 Hz), 7.78 (dd, 1H, J = 8.5 and 8.5 Hz), 7.91 (dd, 1H, 8.5 and 8.5 Hz), 8.32 (d, 1H, J = 8.5), 8.43 (d, 1H, J = 8.5 Hz).
- ^{13}C NMR ($CDCl_3$): 15.87, 124.40, 125.41, 126.30, 129.61, 132.32, 132.52, 137.88, 141.61, 147.05, 148.23, 151.23, 183.43, 186.69
- IR ($CHCl_3$): 1701, 1661 cm^{-1}

D - Preparation of the intermediate products of formula IVa (Scheme II)

D-1 - Synthesis of 6-methyl-1,11-diazanaphthacene-5,12-dione (*Intermediate D_1*)

A solution of 9-methylacridine-1,4-dione (200 mg, 0.896 mmol), acrolein-N,N-dimethylhydrazone (96 mg, 0.984 mmol) and acetic anhydride (1 ml) in 20 ml of CH_2Cl_2 is stirred under N_2 at room temperature for 30 minutes. After concentrating the solvent, the medium is purified by filtration through silica (CH_2Cl_2) to recover the addition product that is not completely aromatic. A suspension of this compound and of 10% Pd/C (20 mg) in 4 ml of toluene is refluxed for 30 minutes. After concentrating, the crude product obtained is purified by flash chromatography on silica (98/2 CH_2Cl_2/MeOH) to give the expected tetracycle in the form of a beige-colored powder (23 mg).

- Yield = 13%
- ^{1}H NMR ($CDCl_3$): 3.32 (s, 3H), 7.78-7.83 (m, 2H), 7.95 (ddd, 1H, J = 8.4, 7.7 and 1.5 Hz), 8.39 (dd, 1H, J =8.8 and 1.5 Hz), 8.51 (dd, 1H, J = 7.7 and 1.5 Hz), 8.68 (dd, 1H, J = 8.1 and 1.9 Hz), 9.16 (dd, 1H, J = 4.8 and 1.9 Hz)

- ^{13}C NMR ($CDCl_3$): 16.67, 124.59, 125.44, 128.39, 129.76, 129.89, 132.25, 132.54, 132.88, 135.93, 148.00, 148.59, 148.73, 152.48, 155.31, 180.81, 184.37
- IR ($CHCl_3$): 1703, 1663 cm^{-1}

D-2 – Synthesis of 3-methoxy-6-methyl-1,11-diazanaphthacene-5,12-dione (*Intermediate D_2*)

3-Methoxy-6-methyl-1,11-diazanaphthacene-5,12-dione is prepared according to the procedure described in D-1, starting with a solution of 9-methylacridine-1,4-dione (Compound 7) (200 mg, 0.896 mmol),2-methoxy-2-propenal-dimethylhydrazone (126 mg, 0.984 mmol) and acetic anhydride (1 ml) in 20 ml of CH_2Cl_2.

__EXAMPLE 1__

5-Methyl-9*H*-quino[4,3,2-de][1,10]phenanthrolin-9-one (CRL 8323)

A solution of the intermediate tetracycle B_1 (1 g, 3.47 mmol) and of dimethylformamide diethyl acetal (2 ml, 10.41 mmol) in 7 ml of DMF is refluxed for 1 hour. After evaporating to dryness, ammonium chloride (2.77 g, 52 mmol) and 50 ml of ethanol are added. The reaction medium is refluxed again for 30 minutes. After evaporating off the solvent, the crude product is taken up in water and extracted 4 times with dichloromethane. The organic phases are dried over $MgSO_4$ and then evaporated. After recrystallization from 125 ml of methanol, 0.7 g of the expected compound CRL 8323 is obtained in the form of a mustard-yellow solid.

- Yield = 67%
- Melting point = 200°C
- ^1H NMR ($CDCl_3$): 2.69 (s, 3H), 7.65 (dd, 1H, J = 8 and 4.8 Hz), 7.81 (dd, 1H, J = 8 and 1.2 Hz), 8.44 (d, 1H, J = 1.2 Hz), 8.49 (d, 1H, J = 8 Hz), 8.50 (d, 1H, J = 5.6 Hz), 8.78 (dd, 1H, J = 2 and 8 Hz), 9.15 (dd, 1H, J = 4.8 and 2 Hz), 9.24 (d, 1H, J = 5.6 Hz)
- ^{13}C NMR ($CDCl_3$): 22.06, 116.54, 117.87, 122.15, 123.12, 125.24, 128.74, 132.58, 133.47, 136.25, 137.19,

141.63, 143.88, 144.79, 149.16, 149.31, 152.09, 155.15, 181.53

- MS (m/z): 297 (17.6), 296 (34.3), 268 (25.4), 149 (50.3)

EXAMPLE 2

5-Chloro-9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one (CRL 8301)

Preparation according to the process described in Example 1, starting with the intermediate tetracycle B_2 (0.25 g, 0.81 mmol) and dimethylformamide diethyl acetal (1.5 ml, 8.75 mmol) in DMF (4.5 ml). Ammonium chloride (2.95 g, 55 mmol), ethanol (50 ml). After purification by flash chromatography (98/2 CH_2Cl_2/MeOH), 60 mg of the expected compound CRL 8301 are obtained in the form of a yellow solid.

- Yield = 23%
- Melting point = 200°C
- ^1H NMR ($CDCl_3$): 7.68 (dd, 1H, J = 8.4 and 4.8 Hz), 7.94 (dd, 1H, J = 8.8 and 2 Hz), 8.46 (d, 1H, J = 5.6 Hz), 8.55 (d, 1H, J = 8.8 Hz), 8.63 (d, 1H, J = 2 Hz), 8.79 (dd, 1H, J = 2 and 8.4 Hz), 9.18 (dd, 1H, J = 4.8 and 2 Hz), 9.30 (d, 1H, J = 5.6 Hz)
- ^{13}C NMR ($CDCl_3$): 117.07, 118.46, 122.98, 124.82, 126.12, 129.34, 133.02, 134.81, 137.00, 137.42, 137.79, 144.45, 146.35, 150.24, 150.45, 152.55, 156.02, 181.9
- MS (m/z): 319 (43), 317 (100), 291 (14.5), 290 (18), 289 (100).

EXAMPLE 3

5-(Benzylamino)-9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one (CRL 8241)

Preparation according to the process described in Example 1, starting with the intermediate tetracycle B_3 (3.58 g, 9.45 mmol) and dimethylformamide diethyl acetal (5.7 ml, 33.26 mmol) in DMF (19 ml). Ammonium chloride (2.95 g, 55 mmol), ethanol (50 ml). After purification by flash chromatography (96/4 CH_2Cl_2/MeOH),

2 g of the expected compound CRL 8241 are obtained in the form of a wine-colored powder.

- Yield = 55%
- Melting point = 219°C
- ^{1}H NMR ($CDCl_3$): 4.61 (d, 2H), 5.10 (t, 1H), 7.31 (dd, 1H, J = 8.8 Hz, J = 2.4 Hz), 7.452-7.327 (m, 5H), 7.55 (d, 1H, J = 2.4 Hz), 7.63 (dd, 1H, J = 4.4 Hz, J = 8.4 Hz), 8.29 (d, 1H, J = 5.2 Hz), 8.36 (d, 1H, J = 8.8 Hz), 8.79 (dd, 1H, J = 1.2 Hz, J = 8.4 Hz), 9.13 (dd, 1H, J = 4.4 and 1.2 Hz), 9.14 (d, 1H, J = 5.2 Hz)
- MS (m/z): 388 (7), 387 (100), 386 (85), 385 (25), 369 (99), 368 (44)

EXAMPLE 4

5-(Dimethylamino)-9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one (CRL 8325)

Preparation according to the process described in Example 1, starting with the intermediate tetracycle B_5 (0.25 g, 0.79 mmol) and dimethylformamide diethyl acetal (0.5 ml, 2.98 mmol) in DMF (5 ml). Ammonium chloride (1 g, 18.7 mmol), ethanol (16 ml). After purification by flash chromatography (100/5 CH_2Cl_2/MeOH), 170 mg of the expected compound CRL 8325 are obtained in the form of a violet powder.

- Yield = 66%
- Melting point = > 260°C
- ^{1}H NMR ($CDCl_3$): 3.25 (s, 6H), 7.45 (dd, 1H, J = 9.2 Hz, J = 3 Hz), 7.57 (d, 1H, J = 3 Hz), 7.63 (dd, 1H, J = 4.4 and 8 Hz), 8.41 (d, 1H, J = 9.2 Hz), 8.43 (d, 1H, J = 5.6 Hz), 8.81 (dd, 1H, J = 2 and 7.6 Hz), 9.13 (dd, 1H, J = 4.4 and 2 Hz), 9.17 (d, 1H, J = 5.6 Hz)
- ^{13}C NMR ($CDCl_3$): 40.45, 100.84, 116.81, 118.69, 118.99, 125.19, 126.10, 129.46, 134.62, 136.03, 136.30, 139.00, 140.69, 148.16, 149.15, 151.53, 152.47, 154.83, 181.65
- MS (m/z): 326 (34.5), 325 (100), 324 (100), 254 (15.5), 253 (13.4).

EXAMPLE 5

5-Methoxy-9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one (CRL 8297)

Preparation according to the process described in Example 1, starting with the intermediate tetracycle B_6 (2 g, 6.57 mmol) and dimethylformamide diethyl acetal (4 ml, 23.34 mmol) in DMF (14 ml). Ammonium chloride (8 g, 149.5 mmol), ethanol (130 ml). After purification by flash chromatography (100/5 CH_2Cl_2/MeOH), 170 mg of the expected compound CRL 8297 are obtained in the form of a greenish solid.

- Yield = 66%
- Melting point = > 260°C
- ^1H NMR ($CDCl_3$): 4.10 (s, 3H), 7.62 (dd, 1H, J = 9.2 Hz, J = 2.4 Hz), 7.66 (dd, 1H, J = 4.4 and 8 Hz), 7.96 (d, 1H, J = 2.4 Hz), 8.48 (d, 1H, J = 2.4 Hz), 8.54 (d, 1H, J = 9.2 Hz), 8.80 (dd, 1H, J = 2.4 and 8 Hz), 9.16 (dd, 1H, J = 4.4 and 2.4 Hz), 9.25 (d, 1H, J = 5.2 Hz)
- ^{13}C NMR ($CDCl_3$): 30.93, 116.86, 118.41, 122.44, 125.56, 129.25, 134.96, 136.55, 137.13, 141.52, 143.67, 149.11, 149.77, 152.37, 155.38, 161.71, 181.93, 207.00
- MS (m/z): 313 (26), 312 (100), 285 (2), 284 (15), 269 (15), 242 (32.5).

EXAMPLE 6

7-Nitro-9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one (CRL 8289)

Ascididemin (2 g, 7.06 mmol) is added portionwise to a mixture of 45 ml of sulfuric acid and 45 ml of nitric acid at 0°C. The reaction medium is heated at 130°C for 2 hours and, after cooling, is then poured into a conical flask containing 400 g of ice. After filtration, a yellow precipitate is obtained, which is rinsed several times with ether. It is then taken up in a 600/1/300 $CH_2Cl_2/NH_4OH/H_2O$ mixture. The organic phase is recovered and the aqueous phase is extracted 3 times with CH_2Cl_2. After drying over $MgSO_4$, the organic phases

are evaporated to give 1.62 g of the expected compound CRL 8289 in the form of a yellow solid.

- Yield = 70%
- Melting point = 224°C
- ^{1}H NMR ($CDCl_3$): 7.69 (dd, 1H, J = 4.4 and 8 Hz), 8.04 (dd, 1H, J = 8 and 8 Hz), 8.28 (dd, 1H, J = 8 Hz), 8.56 (d, 1H, J = 5.2 Hz), 8.75 (dd, 1H, J = 2 and 8 Hz), 8.89 (dd, 1H, J = 1.2 and 8 Hz), 9.18 (dd, 1H, J = 4.4 and 2 Hz), 9.37 (d, 1H, J = 5.6 Hz)
- ^{13}C NMR ($CDCl_3$): 79.20, 117.61, 118.39, 124.21, 124.89, 125.98, 127.54, 129.04, 130.14, 135.62, 136.63, 148.17, 149.76, 149.94, 150.12, 151.66, 154.88, 180.56.
- MS (m/z): 328 (18), 327 (100). 299 (22), 297 (9), 269 (10), 253 (24), 242 (11), 241 (33).

EXAMPLE 7

7-Amino-9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one (CRL 8344)

A suspension of the nitro derivative CRL 8289 (0.4 g, 1.22 mmol) and iron (0.37 g, 6.59 mmol) in a 10/10 AcOH/H_2O mixture is refluxed for 1 hour. EDTA (1.94 g, 6.59 mmol) is added and the reaction medium is then basified with concentrated sodium hydroxide. The mixture is extracted 3 times with CH_2Cl_2. After drying over $MgSO_4$, the organic phases are evaporated to give 0.32 g of the expected compound CRL 8344 in the form of a blue solid.

- Yield = 88%
- Melting point = > 260°C
- ^{1}H NMR ($CDCl_3$): 5.68 (s, 2H), 7.16 (d, 1H, J = 7.8 Hz), 7.66 (dd, 1H, J = 7.6 and 4.8 Hz), 7.69 (dd, 1H, J = 7.8 and 7.8 Hz), 7.91 (d, 1H, J = 7.8 Hz), 8.46 (d, 1H, J = 5.2 Hz), 8.77 (dd, 1H, J = 1.6 and 7.6 Hz), 9.17 (dd, 1H, J = 1.6 and 4.8 Hz), 9.21 (d, 1H, J = 5.2 Hz).
- ^{13}C NMR ($CDCl_3$): 109.42, 112.71, 117.70, 118.43, 124.29, 125.64, 129.12, 132.63, 132.81, 135.53, 137.27, 141.68, 148.68, 148.89, 149.03, 151.96, 154.68, 180.71

- MS (m/z): 298 (34.7), 297 (100), 269 (11), 268 (8).

EXAMPLE 8

5-Bromo-9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one (CRL 8248)

A solution of bromine (0.2 ml, 3.88 mmol) in 5 ml of acetic acid is added dropwise to a solution of ascididemin (0.5 g, 1.77 mmol) in 20 ml of acetic acid. The reaction medium is refluxed (stoppered condensor) for 24 hours. After cooling, the mixture is neutralized with saturated $NaHCO_3$ solution and extracted 4 times with CH_2Cl_2. The organic phases are dried over $MgSO_4$ and then evaporated. The crude product obtained is purified by flash chromatography on a column of silica (96/4 CH_2Cl_2/MeOH) to give 0.548 g of the expected compound CRL 8248 in the form of a yellow solid.

- Yield = 86%
- Melting point = 208°C
- ^1H NMR ($CDCl_3$): 7.68 (dd, 1H, J = 4.4 and 8 Hz), 8.09 (dd, 1H, J = 8.8 Hz, J = 2 Hz), 8.48 (d, 1H, J = 8.8 Hz), 8.49 (d, 1H, J = 6 Hz), 8.79 (dd, 1H, J = 2 and 8 Hz), 8.82 (d, 1H, J = 2 Hz), 9.18 (dd, 1H, J = 2 Hz, J = 4.4 Hz), 9.30 (d, 1H, J = 6 Hz)
- ^{13}C NMR ($CDCl_3$): 116.76, 117.04, 118.26, 124.76, 125.81, 125.93, 129.05, 134.52, 135.43, 136.72, 137.01, 144.41, 146.24, 149.93, 150.12, 152.27, 155.67, 181.69
- MS (m/z): 363 (99), 362 (83), 361 (100), 360 (27), 255 (9), 254 (51).

EXAMPLE 9

5-Amino-9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one (CRL 8347)

Sodium azide (2.34 g, 36.1 mmol) is added to a solution of bromo ascididemin: CRL 8248 (2.3 g, 6.33 mmol) in 460 ml of DMF. The reaction medium is refluxed for 4 hours. After cooling, the mixture is evaporated to dryness and the solid obtained is taken up in water. This mixture is extracted 4 times with CH_2Cl_2. After

drying over $MgSO_4$ and evaporating off the solvent, the crude product is purified by flash chromatography on a column of silica (90/10 $HCCl_3$/MeOH) to give 115 mg of the expected compound CRL 8347 in the form of a black powder.

- Yield = 6%
- Melting point = > 260°C
- ^1H NMR ($CDCl_3$): 7.43 (dd, 1H, J = 8.8 and 2.4 Hz), 7.74 (dd, 1H, J = 4.8 and 8 Hz), 7.81 (d, 1H, J = 2.4 Hz), 8.48 (d, 1H, J = 6 Hz), 8.50 (d, 1H, J = 8.8 Hz), 8.90 (dd, 1H, J = 2 and 8 Hz), 9.25 (dd, 1H, J = 2 and 4.8 Hz), 9.29 (d, 1H, J = 6 Hz)
- ^{13}C NMR (DMSO): 102.26, 117.13, 118.54, 121.62, 123.20, 125.34, 126.11, 129.18, 133.80, 134.83, 135.47, 138.42, 147.65, 148.29, 151.63, 152.39, 154.32, 180.35
- MS (m/z): 298 (32), 297 (100), 269 (4), 268 (0.5)

EXAMPLE 10

10-Methoxy-9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one (CRL 8368)

Preparation according to the procedure described by Y. Kitahara *et al.*, Heterocycles, 1993, 36, 943-946.

EXAMPLE 11

10-Hydroxy-9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one (CRL 8387)

Preparation according to the procedure described by Y. Kitahara *et al.*, Tetrahedron, 1997, 53, 17029-17038.

EXAMPLE 12

9*H*-Quino[4,3,2-*de*][1,10]phenanthrolin-9-imine (CRL 8290)

100 mg (0.353 mmol) of ascididemin are dissolved in a solution containing 5 ml of aqueous ammonia and 2 ml of EtOH. The reaction medium is refluxed (stoppered condensor) for 72 hours. After evaporating off the solvent on a rotary evaporator, the residue is purified

by flash chromatography on alumina (99/1 CH_2Cl_2/MeOH) to give 87 mg of compound CRL 8290.

- Yield = 87%
- Melting point = > 260°C
- ^1H NMR ($CDCl_3$): 7.61 (dd, 1H, J = 5 and 8 Hz), 7.86 (dd, 1H, J = 8 and 8 Hz), 7.97 (dd, 1H, J = 8 and 8 Hz), 8.40 (d, 1H, J = 8 Hz), 8.43 (d, 1H, J = 6 Hz), 8.64 (d, 1H, J = 8 Hz), 9.04 (dd, 1H, J = 8 and 2.5 Hz), 9.08 (dd, 1H, J = 5 and 2.5 Hz), 9.22 (d, 1H, J = 6 Hz), 12.48 (s, 1H)

EXAMPLE 13

9*H*-Quino[4,3,2-*de*][1,10]phenanthrolin-9-oxime (CRL 8292)

500 mg (1.77 mmol) of ascididemin and 500 mg of NH_2OH, 1/2 H_2SO_4 are dissolved in 1 ml of pyridine and 10 ml of EtOH. The reaction medium is refluxed for 48 hours. After evaporating off the solvent on a rotary evaporator, 20 ml of water are added and the medium is extracted with $HCCl_3$ (3 × 20 ml). The organic phases are dried over $MgSO_4$ and then evaporated on a rotary evaporator. The residue is purified by flash chromatography on alumina (99/1 CH_2Cl_2/MeOH) to give 240 mg of the oxime CRL 8292 in the form of a yellow powder.

- Yield = 46%
- Melting point = > 260°C
- ^1H NMR ($CDCl_3$): 7.68 (dd, 1H, J = 4.4 and 8.4 Hz), 7.98 (ddd, 1H, J = 7.6 and 7.6 and 1.6 Hz), 8.07 (ddd, 1H, J = 7.6 and 7.6 and 1.6 Hz), 8.30 (dd, 1H, J = 7.6 and 1.6 Hz), 8.56 (d, 1H, J = 6 Hz), 8.75 (dd, 1H, J = 7.6 and 1.6 Hz), 9.00 (dd, 1H, J = 8.4 and 1.2 Hz), 9.12 (dd, 1H, J = 4.4 and 1.2 Hz), 9.41 (d, 1H, J = 6 Hz)
- ^{13}C NMR ($CDCl_3$): 115.06, 116.14, 123.16, 123.29, 125.46, 128.33, 128.77, 129.54, 131.86, 132.16, 138.48, 140.94, 141.37, 145.82, 146.75, 151.27, 151.65, 151.80
- MS (m/z): 298 (64.5), 268 (100), 266 (21.9)

EXAMPLE 14

10-(2-Acetylanilino)-9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one

(CRL 8333)

Preparation according to the process described in Example 1, starting with the intermediate tetracycle B_7 (0.4 g, 0.98 mmol) and dimethylformamide diethyl acetal (0.6 ml, 3.43 mmol) in DMF (4 ml). Ammonium chloride (1.2 g, 22.4 mmol), ethanol (20 ml). After purification by flash chromatography (100/5 CH_2Cl_2/MeOH), 144 mg of the expected compound CRL 8333 are obtained in the form of a brown-red solid.

- Yield = 35%
- Melting point = > 260°C
- ^{1}H NMR ($CDCl_3$): 2.88 (s, 3H), 3.12 (s, 3H), 5.54 (d, 1H), 7.13 (d, 1H, J = 6 Hz), 7.30 (ddd, 1H, J = 7.6 and 7.6 and 1.2 Hz), 7.45 (ddd, 1H, J = 7.6 and 7.6 and 1.2 Hz), 7.51 (d, 1H, J = 7.6 Hz), 7.65 (broad s, 1H), 7.69 (d, 1H, J = 7.6 Hz), 7.88 (ddd, 1H, J = 7.6 and 7.6 and 1.2 Hz), 7.96 (ddd, 1H, J = 7.6 and 7.6 and 1.2 Hz), 8.48 (d, 1H, J = 6 Hz), 8.51 (d, 1H, J = 6 Hz), 8.57 (dd, 1H, J = 7.6 and 1.2 Hz), 8.64 (dd, 1H, J = 7.6 and 1.2 Hz), 9.23 (d, 1H, J = 6 Hz)
- ^{13}C NMR ($CDCl_3$): 37.22, 45.05, 109.94, 113.94, 116.56, 117.38, 122.92, 123.34, 125.43, 125.90, 129.47, 130.27, 131.61, 132.94, 135.87, 137.17, 137.57, 145.87, 146.93, 149.81, 150.28, 153.30, 154.27, 154.54, 154.61, 183.73

EXAMPLE 15

10-Hydroxy-9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one diiodide

(CRL 8369)

500 mg (1.597 mmol) of the compound of Example 10 (CRL 8368) and 40 ml of acetic acid in 100 ml of hydriodic acid (57%) are heated at 100°C for 30 minutes. After cooling, the reaction medium is poured into 500 ml of water and ice is added, followed by neutralization with $NaHCO_3$ (solid). After several

extractions with a mixture of 5% MeOH in $HCCl_3$ (6 times 500 ml), the organic phases are dried over $MgSO_4$ and then concentrated on a rotary evaporator to give 0.36 g of compound CRL 8369 in the form of a wine-colored powder.

- Yield = 41%
- Melting point = > 260°C
- ^1H NMR (DMSO): 6.24 (d, 1H, J = 7.6 Hz), 6.86 (td, 1H, J = 8 and 4 Hz), 7.27 (d, 2H, J = 4 Hz), 7.57 (d, 1H, J = 5.2 Hz), 7.89 (d, 1H, J = 8 Hz), 7.93 (dd, 1H, J = 7.6 and 7.6 Hz), 8.51 (d, 1H, J = 5.2 Hz), 9.54 (s, 1H), 12.62 (broad m, 1H), 14.42 (s, 1H)
- ^{13}C NMR (DMSO): 107.81, 109.87, 114.24, 115.36, 116.31, 117.33, 120.11, 120.97, 124.14, 127.63, 132.18, 132.81, 134.89, 139.24, 139.35, 141.15, 148.72, 181.29

EXAMPLE 16

10-Chloro-9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one (CRL 8373)

50 mg (0.09 mmol) of the salt of Example 15 (CRL 8369) dissolved in 4 ml of $POCl_3$ are refluxed for 2 hours. After evaporating off the $POCl_3$ on a rotary evaporator, the reaction medium is neutralized with saturated $NaHCO_3$ solution. After several extractions with a mixture of 5% MeOH in $HCCl_3$ (5 times 20 ml), the organic phases are dried over $MgSO_4$ and then concentrated on a rotary evaporator. The residue obtained is purified by flash chromatography on a column of silica (95/5 CH_2Cl_2/MeOH) to give 20 mg of the expected compound CRL 8373 in the form of a yellow powder.

- Yield = 77%
- Melting point = > 260°C
- ^1H NMR ($CDCl_3$): 7.67 (d, 1H, J = 5.6 Hz), 7.95 (ddd, 1H, J = 8 and 8 and 0.8 Hz), 8.03 (ddd, 1H, J = 8 and 8 and 1.2 Hz), 8.57 (d, 1H, J = 5.6 Hz), 8.61 (ddd, 1H, J = 8 and 1.2 Hz), 8.68 (ddd, 1H, J = 8 and 0.8 Hz), 8.97 (d, 1H, J = 5.6 Hz), 9.30 (d, 1H, J = 5.6 Hz)

• ^{13}C NMR ($CDCl_3$): 117.60, 117.84, 123.31, 123.60, 126.69, 129.10, 131.17, 132.38, 133.47, 138.21, 146.24, 146.51, 147.26, 149.40, 150.32, 154.30, 154.94, 180.47

• MS (m/z): 318 (9.6), 316 (70.2), 290 (29.6), 288 (100), 255 (23.4), 253 (26.8).

EXAMPLE 17

5-Bromo-10-methoxy-9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one

(CRL 8389)

Preparation according to the process described in Example 1, starting with the intermediate tetracycle B_8 (0.74 g, 1.93 mmol) and dimethylformamide diethyl acetal (1.3 ml, 7.24 mmol) in 15 ml of DMF. Ammonium chloride (1.96 g, 36.4 mmol), ethanol (200 ml). After purification by flash chromatography (95/5 CH_2Cl_2/MeOH), 210 mg of the expected compound CRL 8389 are obtained in the form of an orange powder.

• Yield = 42%

• Melting point = > 260°C

• ^{1}H NMR ($CDCl_3$): 4.14 (s, 3H), 7.14 (d, 1H, J = 5.6 Hz), 8.05 (dd, 1H, J = 2 and 8.8 Hz), 8.43 (d, 1H, J = 6 Hz), 8.44 (d, 1H, J = 8.8 Hz), 8.76 (d, 1H, J = 2 Hz), 8.95 (d, 1H, J = 6 Hz), 9.27 (d, 1H, J = 5.6 Hz)

• ^{13}C NMR ($CDCl_3$): 57.12, 109.52, 117.00, 117.76, 119.46, 121.58, 124.81, 125.52, 134.72, 135.49, 137.00, 144.85, 146.51, 147.24, 147.92, 150.43, 156.21, 167.98, 180.57

• MS (m/z): 393 (100), 392 (61.7), 391 (99.2), 390 (17.4), 362 (9.2), 333 (9.8), 254 (34.5).

EXAMPLE 18

5-Amino-11-methoxy-9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one

(CRL 8389)

A solution of compound CRL 8389 (0.5 g, 1.3 mmol) and NaN_3 (0.5 g, 7.7 mmol) in 20 ml of DMF is heated at 90°C for 10 hours. After concentrating, the residue is

taken up in 1N KOH (35 ml) and then extracted with 95/5 CH_2Cl_2/MeOH (4 × 200 ml). After drying over $MgSO_4$ and concentrating on a rotary evaporator, the crude product obtained is purified by flash chromatography on silica (80/20 CH_2Cl_2/MeOH) to give the expected compound CRL 8389 in the form of a violet powder (65 mg).

- Yield = 15%
- Melting point = > 260°C
- ^{1}H NMR (DMSO-d_6)): 4.07 (s, 3H), 6.62 (s, 2H), 7.36 (d, 1H, J = 8.8 Hz), 7.41 (d, 1H, J = 5.9 Hz), 7.74 (s, 1H), 8.08 (d, 1H, J = 8.8 Hz), 8.48 (d, 1H, J = 5.2 Hz), 8.86 (d, 1H, J = 5.9 Hz), 9.08 (d, 1H, J = 5.2 Hz)
- IR (KBr): 3420, 3196, 1636, 1616 cm^{-1}

EXAMPLE 19

5-Amino-9*H*-quino[4,3,2-de][1,10]phenanthrolin-9-one hydrochloride (CRL 8406)

A solution of 5-amino-9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one (1 g, 3.35 mmol) and concentrated HCl (0.56 ml) in 200 ml of methanol is stirred at room temperature for 1 hour. 200 ml of ether are added and, after leaving the salt to precipitate out, the medium is filtered to recover the expected compound CRL 8406 in the form of a black powder (1 g).

- Yield = 90%
- ^{1}H NMR (DMSO-d_6): 7.44 (dd, 1H, J = 8.8 and 2.2 Hz), 7.81 (d, 1H, J = 2.2 Hz), 7.93 (dd, 1H, J = 5.6 and 5.9 Hz), 8.12 (d, 1H, J = 8.8 Hz), 8.66 (d, 1H, J = 5.6 Hz), 8.75 (d, 1H, J = 5.9 Hz), 9.07 (d, 1H, J = 5.9 Hz), 9.14 (d, 1H, J = 5.9 Hz)
- IR (KBr): 3404, 3287, 3170, 1691, 1676, 1649 cm^{-1}

EXAMPLE 20

5-(Dimethylamino)-9*H*-quino[4,3,2-de][1,10]phenanthrolin-9-one hydrochloride (CRL 8407)

A solution of 5-(dimethylamino)-9*H*-quino[4,3,2-*de*]-[1,10]phenanthrolin-9-one (1 g, 3.06 mmol) and

concentrated HCl (0.3 ml) in 120 ml of $CHCl_3$ is stirred at room temperature for 45 minutes. After addition of 350 ml of ether, followed by precipitation of the salt, the medium is filtered to recover the expected product in the form of a navy blue powder (0.97 g).

- Yield = 87%
- Melting point = > 260°C

EXAMPLE 21

5-(Benzylamino)-9*H*-quino[4,3,2-de][1,10]phenanthrolin-9-one hydrochloride (CRL 8416)

A solution of 5-(benzylamino)-9*H*-quino[4,3,2-*de*][1,10]-phenanthrolin-9-one ASC20 (0.94 g, 2.42 mmol) and concentrated HCl (0.2 ml) in 40 ml of $CHCl_3$ is stirred at room temperature for 30 minutes. The solvent is evaporated off and 150 ml of ether are added and, after leaving the salt to precipitate out, the medium is filtered to recover the expected compound CRL 8416 in the form of a black powder (0.98 g).

- Yield = 95%
- Melting point = > 260°C

EXAMPLE 22

5-(Dimethylamino-2-ethyl)amino-9*H*-quino[4,3,2-de]-[1,10]phenanthrolin-9-one (CRL 8419)

25 ml (166 mmol) of trifluoroacetic acid are added to a mixture of compound CRL 8347 (2.56 g, 8.59 mmol) and dimethylformamide diethyl acetal (7.9 ml, 43.3 mmol) at 0°C. The reaction medium is stirred for 5 minutes and sodium cyanoborohydride (8.2 g, 130 mmol) is then added portionwise. The reaction medium is then heated and maintained at 95°C. After 18 hours, the mixture is basified to pH 8 with saturated $NaHCO_3$ solution (about 600 ml) and then extracted with 95/5 $CHCl_3$/MeOH (3 × 800 ml). The organic phases are washed with water and then dried over $MgSO_4$. After evaporating off the solvent on a rotary evaporator, the crude product obtained is purified by filtration through alumina ($CHCl_3$ and then 95 $CHCl_3$/MeOH) to give 1.15 g of the

expected compound CRL 8419 in the form of a black powder.

- Yield = 36%
- Melting point: decomposes before melting
- ^{1}H NMR ($CDCl_3$): 2.37 (s, 6H), 2.62 (t, 2H, J = 7.32 Hz), 3.70 (t, 2H, J = 7.32 Hz), 7.39 (dd, 1H, J = 9.2 and 3 Hz), 7.62 (dd, 1H, J = 8.0 and 4.5 Hz), 7.66 (d, 1H, J = 3 Hz), 8.35 (d, 1H, J = 9.2 Hz), 8.38 (d, 1H, J = 5.7 Hz), 8.79 (dd, 1H, J = 8.0 and 1.8 Hz), 9.12 (dd, 1H, J = 4.5 and 1.8 Hz), 9.15 (d, 1H, J = 5.7 Hz)
- ^{13}C NMR ($CDCl_3$): 45.97, 50.31, 56.40, 101.05, 116.81, 118.48, 118.89, 125.22, 126.30, 129.35, 134.87, 135.97, 136.32, 138.91, 140.55, 148.25, 148.98, 149.69, 152.23, 154.82, 181.37
- IR ($CHCl_3$): 1663 cm^{-1}
- MS (m/z): 369 (100), 354 (15), 236 (37)

EXAMPLE 23

5-(Dimethylamino-2-ethyl)amino-9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one hydrochloride (CRL 8418)

265 µl (3.25 mmol) of concentrated hydrochloric acid are added to 1.2 g (3.25 mmol) of compound CRL 8419 dissolved in 60 ml of chloroform. The reaction medium is stirred for 2 hours at room temperature. The precipitate formed is filtered off and then washed with ether. Compound CRL 8418 (0.93 g) is obtained in the form of a black powder.

- Yield = 70%
- ^{1}H NMR (DMSO-d_6): 2.67 (s, 6H), 3.09 (m, 2H), 4.01 (m, 2H), 7.67 (dm, 1H, J = 9.2 Hz), 7.80 (dd, 1H, J = 8,0 and 4.5 Hz), 7.94 (m, 1H), 8.26 (d, 1H, J = 9.2 Hz), 8.64 (d, 1H, J = 5.7 Hz), 9.09 (m, 1H), 9.12 (dd, 1H, J = 4.5 and 1.8 Hz), 9.14 (d, 1H, J = 5.7 Hz).

EXAMPLE 24

5-Bis(2-chloroethyl)amino-9*H*-quino[4,3,2-*de*][1,10]-phenanthrolin-9-one

(CRL 8422)

10 mmol of sodium cyanoborohydride $NaBH_3CN$ (0.63 g) are added portionwise to a solution of 5-amino-9*H*-quino-[4,3,2-*de*][1,10]phenanthrolin-9-one (1 g, 3.95 mmol) and chloroacetaldehyde (50% aqueous, 2.6 ml, 16.8 mmol) in acetic acid (30 ml), at 0°C. The reaction medium is stirred at 0°C for 5 minutes and then at room temperature for 30 minutes. Next, the medium is basified with saturated sodium hydrogen carbonate $NaHCO_3$ solution and then extracted with a 95/5 $CHCl_3$/MeOH mixture. The organic phases are dried over magnesium sulfate $MgSO_4$ and concentrated on a rotary evaporator. The crude product obtained is purified by filtration through silica ($CHCl_3$ and then 99/1 $CHCl_3$/MeOH) to give two compounds: CRL 8422 and CRL 8423 (described in Example 25).

5-Bis(chloroethyl)amino-9H-quino[4,3,2-*de*][1,10]phenanthrolin-9-one (CRL 8422) was obtained in the form of a pink powder (0.14 g):

- Yield = 10%
- Melting point = 220°C
- IR (KBr): 1666, 1650 cm^{-1}
- ^1H NMR ($CDCl_3$): 3.83 (t, 4H, J = 7.0 Hz), 4.04 (t, 4H, J = 7.0 Hz), 7.47 (dd, 1H, J = 9.5 and 2.9 Hz), 7.66 (dd, 1H, J = 8.0 and 4.4 Hz), 7.70 (d, 1H, J = 2.9 Hz), 8.42 (d, 1H, J = 5.6 Hz), 8.50 (d, 1H, J = 9.5 Hz), 8.81 (dd, 1H, J = 8.0 and 1.8 Hz), 9.16 (dd, 1H, J = 4.4 and 1.8 Hz), 9.23 (d, 1H, J = 5.6 Hz)
- ^{13}C NMR ($CDCl_3$): 40.16, 53.60, 101.70, 116.60, 118.37, 118.68, 125.39, 125.91, 129.25, 135.13, 136.12, 136.38, 139.42, 141.93, 148.24, 148.73, 149.34, 152.22, 155.08, 181.43.

EXAMPLE 25

5-(2-chloroethyl)amino-9*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one (CRL 8423)

According to the process described in Example 24, 0.22 g of compound CRL 8423 are obtained in the form of

a violet powder. The characteristics of compound CRL 8423 are as follows:

- Yield = 18%
- Melting point = 196°C
- IR (KBr): 3413, 3275, 1654, 1617 cm^{-1}
- ^{1}H NMR ($CDCl_3$): 3.81 (t, 2H, J = 5.5 Hz), 3.88 (t, 2H, J = 5.5 Hz), 5.01 (broad s, 1H), 7.34 (dd, 1H, J = 8.8 and 2.5 Hz), 7.60 (d, 1H, J = 2.5 Hz), 7.65 (dd, 1H, J = 7.5 and 4.4 Hz), 8.41 (d, 1H, J = 5.8 Hz), 8.43 (d, 1H, J = 8.8 Hz), 8.82 (dd, 1H, J = 7.5 and 1.5 Hz), 9.15 (dd, 1H, J = 4.4 and 1.5 Hz), 9.21 (dd, 1H, J = 5.8 Hz)
- ^{13}C NMR ($CDCl_3$): 42.83, 45.01, 100.76, 116.81, 118.78, 120.85, 125.38, 126.35, 129.35, 135.04, 136.04, 136.43, 140.22, 141.56, 148.49 (2C), 149.41, 152.30, 155.07, 181.57.

EXAMPLE 26

12-Methoxy-9-*H*-quino[4,3,2-*de*][1,10]phenanthrolin-9-one (CRL 8472)

0.54 ml (3 mmol) of dimethylformamide diethyl acetal is added to a suspension of 2-methoxy-11-methyl-1,6-diazanaphthacene-5,12-dione (*Intermediate* B_9) (0.23 g, 0.75 mmol) in DMF (7 ml) under N_2. The reaction medium is heated at 120°C for 1 hour. After concentrating under vacuum, ethanol (45 ml) and NH_4Cl (0.46 g) are added and the mixture is then refluxed for 30 minutes. After concentrating on a rotary evaporator, 30 ml of water are added and the medium is then extracted with $CHCl_3$ (2 × 30 ml). The organic phases are dried over $MgSO_4$ and concentrated. The crude product obtained is purified by flash chromatography on silica ($CHCl_3$) to give the expected compound CRL 8472 in the form of a brown powder (50 mg).

- Yield = 21%
- Melting point = > 260°C
- ^{1}H NMR ($CDCl_3$): 4.31 (s, 3H), 7.04 (d, 1H, J = 8.5 Hz), 7.92 (ddd, 1H, J = 8.1, 7.0 and 1.5 Hz), 8.00 (ddd, 1H, J = 8.4, 7.0 and 1.5 Hz), 8.52 (d, 1H, J =

5.5 Hz), 8.63 (dd, 1H, J = 8.1 and 1.5 Hz), 8.66 (d, 1H, J = 8.5 Hz), 8.67 (dd, 1H, J = 8.4 and 1.5 Hz), 9.27 (d, 1H, J = 5.5 Hz)

- ^{13}C NMR ($CDCl_3$): 54.69, 114.43, 116.75, 118.15, 122.92, 123.41, 124.51, 130.62, 131.81, 133.15, 137.86, 139.17, 145.80, 146.28, 149.59, 149.99, 152.24, 167.75, 181.04
- IR ($CHCl_3$):1671, 1588 cm^{-1}
- MS (m/z): 313 (50), 312 (91), 284 (17), 283 (100), 254 (23), 193 (51).

EXAMPLE 27

4-Bromo-5-amino-9-*H*-quino[4,3,2-de][1,10]phenanthrolin-9-one (CRL 8478)

Bromine (35 µl, 0.67 mmol) is added to a suspension of compound CRL 8347 (0.2 g, 0.67 mmol) in acetic acid (8 ml). The reaction medium is heated at 50°C for 6 hours. After concentrating, the medium is basified with 5N sodium hydroxide (20 ml) and then extracted with a 5% MeOH/$CHCl_3$ mixture (400 ml). After drying over $MgSO_4$ and evaporating off the solvent, compound CRL 8478 is obtained in the form of a violet powder which is recrystallized from a 20 ml/15 ml $CHCl_3$/pentane mixture (152 mg).

- Yield = 61%
- Melting point = > 260°C
- ^1H NMR (DMSO-d_6): 7.07 (broad s, 2H), 7.61 (d, 1H, J = 8.8 Hz), 7.77 (dd, 1H, J = 7.7 and 4.0 Hz), 8.18 (d, 1H, J = 8.8 Hz), 8.61 (d, 1H, J = 7.7 Hz), 9.10 (d, 1H, J = 4.0 Hz), 9.14 (d, 1H, J = 5.9 Hz), 9.91 (d, 1H, J = 5.9 Hz)
- IR ($CHCl_3$): 3501, 3400, 1673 cm^{-1}
- MS (m/z): 378 (42), 377 (100), 376 (48), 375 (27)

EXAMPLE 28

11-Acetoxymethyl-9-*H*-quino[4,3,2-de][1,10]phenanthrolin-9-one (CRL 8528)

Dimethylformamide diethyl acetal (0.27 ml, 1.5 mmol) is added to a suspension of 3-acetoxymethyl-11-methyl-1,6-diazanaphthacene-5,12-dione (*Intermediate B_{10}*) (0.11 g, 0.31 mmol) in DMF (4 ml) under N_2. The reaction medium is heated at 120°C for 1 hour. After concentrating under vacuum, ethanol (25 ml) and NH_4Cl (0.23 g) are added and the mixture is then refluxed for 30 minutes. After concentrating on a rotary evaporator, 30 ml of water are added and the medium is then extracted with $CHCl_3$ (2 × 30 ml). The organic phases are dried over $MgSO_4$. After evaporating off the solvent on a rotary evaporator and purification by flash chromatography on silica ($CHCl_3$), 65 mg of compound CRL 8528 are obtained.

- Yield = 60%
- Melting point = 206-210°C
- ^1H NMR ($CDCl_3$): 2.19 (s, 3H), 5.32 (s, 2H), 7.96 (ddd, 1H, J = 1, 1.8 and 8 Hz), 8.03 (ddd, 1H, J = 1, 1.8 and 8.4 Hz), 8.56 (d, 1H, J = 5.5 Hz), 8.64 (dd, 1H, J = 1.1 and 8.4 Hz), 8.71 (dd, 1H, J = 1.1 and 8.0 Hz), 8.77 (d, 1H, J = 2.4 Hz), 9.14 (d, 1H, J = 2.4 Hz), 9.28 (d, 1H, J = 5.5 Hz)
- MS (m/z): 355 (88), 313 (100), 296 (25), 267 (7).

EXAMPLE 29

9-*H*-Quino[4,3,2-de][1,7]phenanthrolin-9-one (CRL 8529)

Dimethylformamide diethyl acetal (0.15 ml, 0.875 mmol) is added to a suspension of 6-methyl-1,11-diazanaphthacene-5,12-dione (*Intermediate D_1*) (52 mg, 0.875 ml) under N_2. The reaction medium is heated at 120°C for 30 minutes. After concentrating under vacuum, ethanol (60 ml) and NH_4Cl (0.34 g) are added and the mixture is refluxed for 30 minutes. After concentrating on a rotary evaporator, 10 ml of water are added and the medium is then extracted with CH_2Cl_2 (2 × 10 ml). The organic phases are dried over $MgSO_4$ and concentrated. The crude product obtained is purified by flash chromatography on silica (99/1 CH_2Cl_2/MeOH) to

give the expected compound CRL 8529 in the form of a yellow solid (6 mg).

- Yield = 11%
- ^{1}H NMR ($CDCl_3$): 7.78 (dd, 1H, J = 8.1 and 4.8 Hz), 7.97 (ddd, 1H, J = 8.0, 7.4 and 1.2 Hz), 8.04 (ddd, 1H, J = 8.0, 7.4 and 1.2 Hz), 8.51 (d, 1H, J = 5.9 Hz), 8.69 (dd, 2H, J = 8.0 and 1.5 Hz), 9.08 (dd, 1H, J = 4.8 and 1.9 Hz), 9.13 (d, 1H, J = 5.9 Hz), 9.27 (d, 1H, J = 1.9 and 8.1 Hz)
- ^{13}C NMR ($CDCl_3$): 115.15, 121.76, 122.28, 127.13, 127.16, 129.65, 130.82, 132.21, 132.60, 132.99, 136.88, 139.91, 144.85, 148.00, 148.03, 151.75, 151.84, 179.94
- MS (m/z): 283 (54), 255 (100) 228 (10).

EXAMPLE 30

5-Bromo-9-*H*-quino[4,3,2-de][1,7]phenanthrolin-9-one (CRL 8839)

Compound CRL 8839 is prepared according to the procedure described in Example 8, starting with 9-*H*-quino[4,3,2-*de*][1,7]phenanthrolin-9-one (CRL 8529) (0.5 g, 1.77 mmol); 20 ml of acetic acid; bromine solution (0.2 ml, 3.88 mmol/5 ml of acetic acid); reflux for 24 hours.

EXAMPLE 31

5-Amino-9-*H*-quino[4,3,2-de][1,7]phenanthrolin-9-one (CRL 8836)

Compound CRL 8836 is prepared according to the procedure described in Example 9, starting with 5-bromo-9-*H*-quino[4,3,2-*de*][1,7]phenanthrolin-9-one (CRL 8839) (1.15 g, 18 mmol); 250 ml of DMF; sodium azide (1.2 g, 1.85 mmol); reflux for 4 hours.

EXAMPLE 32

5-(Dimethylamino-2-ethyl)amino-9-*H*-quino[4,3,2-de]-[1,7]phenanthrolin-9-one (CRL 8840)

Compound CRL 8840 is prepared according to the procedure described in Example 22, starting with 5-amino-9-*H*-quino[4,3,2-*de*][1,7]phenanthrolin-9-one

(CRL 8836) (1.28 g, 4.3 mmol); dimethylformamide diacetal (4 ml, 21.9 mmol); trifluoroacetic acid (12.5 ml, 83 mmol); sodium cyanoborohydride (4.1 g, 65 mmol); 90°C for 8 hours.

EXAMPLE 33

5-Bis(chloroethylamino-2-ethyl)amino-9-*H*-quino[4,3,2-de][1,7]phenanthrolin-9-one (CRL 8841)

Compound CRL 8841 is prepared according to the procedure described in Example 24, starting with 5-amino-9-*H*-quino[4,3,2-*de*][1,7]phenanthrolin-9-one (CRL 8836) (1 g, 3.95 mmol); chloroacetaldehyde (2.6 ml, 16.8 mmol); acetic acid (30 ml); sodium cyanoborohydride (0.63 g, 10 mmol); 30 minutes at room temperature.

EXAMPLE 34

5-(Chloroethylamino-2-ethyl)amino-9-*H*-quino[4,3,2-de]-[1,7]phenanthrolin-9-one (CRL 8842)

Compound CRL 8842 is also obtained during the procedure described in the above example from 5-amino-9-*H*-quino-[4,3,2-*de*][1,7]phenanthrolin-9-one (CRL 8836).

EXAMPLE 35

4-Bromo-5-amino-9-*H*-quino[4,3,2-de][1,7]phenanthrolin-9-one (CRL 8843)

Compound CRL 8843 is prepared according to the procedure described in Example 27, starting with 5-amino-9-*H*-quino[4,3,2-*de*][1,7]phenanthrolin-9-one (CRL 8836) (0.6 g, 2.01 mmol); 24 ml of acetic acid; bromine (35 µl, 0.67 mmol); 50°C for 6 hours.

EXAMPLE 36

7-Nitro-9-*H*-quino[4,3,2-de][1,7]phenanthrolin-9-one (CRL 8838)

Compound CRL 8838 is prepared according to the procedure described in Example 6, starting with 9-*H*-quino[4,3,2-*de*][1,7]phenanthrolin-9-one (CRL 8529)

(1 g, 3.53 mmol); 23 ml of sulfuric acid and 23 ml of nitric acid; 130°C for 2 hours.

EXAMPLE 37

7-Amino-9-*H*-quino[4,3,2-de][1,7]phenanthrolin-9-one (CRL 8837)

Compound CRL 8837 is prepared according to the procedure described in Example 7, starting with 7-nitro-9-*H*-quino[4,3,2-*de*][1,7]phenanthrolin-9-one (CRL 8838) (0.2 g, 0.61 mmol); iron (0.19 g, 3.38 mmol), 10 ml of acetic acid/water mixture (50/50).

EXAMPLE 38

12-Methoxy-9-*H*-quino[4,3,2-de][1,7]phenanthrolin-9-one (CRL 8844)

Compound CRL 8844 is prepared according to the procedure described in Example 29, starting with 3-methoxy-6-methyl-1,11-diazanaphthacene-5,12-dione (*Intermediate D_2*) (0.76 g, 25 mmol); dimethylformamide diacetal (2 ml, 11.67 mmol); 120°C for 30 minutes; NH_4Cl (4.5 g); 500 ml of ethanol; refluxed for 30 minutes.

The results of the pharmacological tests, presented below, demonstrate the cytotoxic qualities of the compounds of formulae I and Ia, and also the maximum tolerated doses. These data enable the therapeutic value of the claimed compounds to be assessed.

1 - Determination of the maximum tolerated dose (MTD)

The evaluation of the maximum tolerated dose was performed on 4- to 6-week-old B6D2F1/Jico mice. The compounds were administered intraperitoneally at increasing doses ranging from 2.5 to 160 mg/kg. The value of the MTD (expressed in mg/kg) is determined from the observation of the survival rate of the

animals over a 14-day period after a single administration of the products under consideration. The change in the weight of the animals is also monitored during this period. When the value of the MTD is greater than 160 mg/kg, the value of the MTD is considered as 160 mg/kg by default.

The results of the estimation of the maximum tolerated dose (MTD) are collated in Table I below:

TABLE I

Compounds CRL	MTD (mg/kg)
CRL 8274 (Ascididemin)	20
CRL 8269 (2-bromoleptoclinidone)	40
CRL 8323 (Example 1)	20
CRL 8301 (Example 2)	> 160
CRL 8241 (Example 3)	> 160
CRL 8325 (Example 4)	> 160
CRL 8297 (Example 5)	> 160
CRL 8289 (Example 6)	20
CRL 8344 (Example 7)	> 160
CRL 8248 (Example 8)	> 160
CRL 8347 (Example 9)	> 160
CRL 8292 (Example 13)	> 160
CRL 8290 (Example 12)	80
CRL 8333 (Example 14)	> 160
CRL 8368 (Example 10)	> 160
CRL 8369 (Example 15)	> 160
CRL 8373 (Example 16)	> 160
CRL 8387 (Example 11)	> 160
CRL 8389 (Example 17)	> 160
CRL 8406 (Example 19)	> 160
CRL 8407 (Example 20)	> 160
CRL 8416 (Example 21)	> 160
CRL 8419 (Example 22)	40
CRL 8418 (Example 23)	40
CRL 8422 (Example 24)	> 160
CRL 8423 (Example 25)	> 160

The majority of the products described in the family of ascididemin or of its isomer do not show any direct toxicity (MTD > 160 mg/kg) and may thus be used *in vivo* at high tissue concentrations, and thus at high doses.

2 - Cytotoxic activity on tumor cell lines in culture

The influence of the compounds of formulae I and Ia on neoplastic cells was evaluated using the MTT colorimetric test. The principle of the MTT test is based on the mitochondrial reduction by metabolically active live cells of the yellow product MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) into a blue product, formazan. The amount of formazan thus obtained is directly proportional to the amount of live cells present in the culture well(s). This amount of formazan is measured by spectrophotometry.

The cell lines are maintained as a monolayer culture at 37°C in closed culture dishes containing MEM 25 MM HEPES base medium (minimum essential medium). This medium, adapted to the growth of a varied range of mammalian diploid or primary cells, is then supplemented:

- with an amount of 5% FCS (Fetal Calf Serum) decomplemented at 56°C for 1 hour,
- with 0.6 mg/ml of L-glutamine,
- with 200 IU/ml of penicillin,
- with 200 mg/ml of streptomycin,
- with 0.1 mg/ml of gentamycin.

The 12 human cancer cell lines used were obtained from the *American Type Culture Collection* (ATCC, Rockville, MD, USA). These 12 cell lines are:

- U-373MG (code ATCC: HTB-17) and U-87MG (code ATCC: HTB-14) which are two glioblastomas,
- SW1088 (code ATCC: HTB-12) which is an astrocytoma,
- A549 (code ATCC: CCL-185) and A-427 (code ATCC: HTB-53) which are two non-small-cell lung cancers,

- HCT-15 (code ATCC: CCL-225) and LoVo (code ATCC: CCL-229) which are two colorectal cancers,
- T-47D (code ATCC: HTB-133) and MCF7 (code ATCC: HTB-22) which are two breast cancers,
- J82 (code ATCC: HTB-1) and T24 (code ATCC: HTB-4) which are two bladder cancers,
- PC-3 (code ATCC: CRL-1435) which is a prostate cancer.

Experimentally: 100 µl of a cell suspension containing 20 000 to 50 000 (depending on the cell type used) cells/mL of culture medium are inoculated in flat-bottomed 96-well multi-well plates and are incubated at 37°C under an atmosphere comprising 5% CO_2 and 70% humidity. After incubating for 24 hours, the culture medium is replaced with 100 µl of fresh medium containing either the various test compounds at concentrations ranging from 10^{-5} to 10^{-10} M or the solvent used to dissolve the test products (control condition). After incubating for 72 hours under the above conditions, the culture medium is replaced with 100 µl of a yellowish solution of MTT dissolved at a rate of 1 mg/mL in RPMI 1640. The microplates are reincubated for 3 hours at 37°C and then centrifuged for 10 minutes at 400 g. The yellowish solution of MTT is removed and the blue formazan crystals formed at the cellular level are dissolved in 100 µl of DMSO. The microplates are then agitated for 5 minutes. The intensity of the resulting blue coloration, and thus of the conversion of the yellow MTT product into blue formazan by the cells that are still alive at the end of the experiment is quantified by spectrophotometry using a *Dynatech Immunoassay System* machine at wavelengths of 570 nm and 630 nm corresponding, respectively, to the maximum absorption wavelengths of formazan and to the background noise. Software built into the spectrophotometer calculates the average

optical density values and also the standard deviation (Std. Dev.) and standard error of mean (SEM) values.

The inhibitory activity on the cell growth of the compounds of formulae I and Ia on the different tumor cell lines was compared with that of the natural product ascididemin (CRL 8274). All of the compounds show significant inhibitory activity on the cell proliferation of the 12 human tumor lines: U-87MG, U-373MG, SW 1088, T24, J82, HCT-15, LoVo, MCF7, T-47D, A549, A-427 and PC-3 with a 50% inhibitory concentration (IC_{50}) which is between 10^{-6}M and 10^{-10}M, depending on the compounds and the tumor lines tested. By way of example, the values of the concentrations flanking the IC_{50} values which are obtained on the various cell lines are given in Table II:

TABLE II

COMPOUNDS	CELL LINES											
CRL	U-87MG	U-373MG	SW1088	T24	J82	HCT-15	LoVo	MCF7	T-47D	A549	A-427	PC-3
CRL8274	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-8},10^{-9}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-8},10^{-9}[$
CRL8289	$]10^{-8},10^{-9}[$	$]10^{-8},10^{-9}[$	$]10^{-8},10^{-9}[$	$]10^{-8},10^{-9}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-8},10^{-9}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-8},10^{-9}[$	$]10^{-6},10^{-7}[$
CRL8248	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$
CRL8241	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$
CRL8297	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$
CRL8301	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$
CRL8323	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$
CRL8325	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-8},10^{-9}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-8},10^{-9}[$	$]10^{-7},10^{-8}[$
CRL8344	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-5},10^{-6}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$
CRL8347	$]10^{-7},10^{-8}[$	$]10^{-8},10^{-9}[$	$]10^{-7},10^{-8}[$	$]10^{-8},10^{-9}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-5},10^{-6}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-8},10^{-9}[$	$]10^{-8},10^{-9}[$	$]10^{-6},10^{-7}[$
CRL8368	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-5},10^{-6}[$	$]10^{-6},10^{-7}[$	$]10^{-5},10^{-6}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6}\ 10^{-7}[$
CRL8369	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-6},10^{-7}[$	$]10^{-5},10^{-6}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-5},10^{-6}[$	$]10^{-6},10^{-7}[$	$]10^{-5},10^{-6}[$
CRL8373	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-5},10^{-6}[$	$]10^{-6},10^{-7}[$	$]10^{-5},10^{-6}[$
CRL8387	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-6},10^{-7}[$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-6},10^{-7}[$	$]10^{-5}[$
CRL8389	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-5},10^{-6}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$
CRL8268*	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$>10^{-5}$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-6},10^{-7}[$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$
CRL8322*	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$>10^{-5}$	$>10^{-5}$	$>10^{-5}$	$]10^{-5},10^{-6}[$	$>10^{-5}$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$>10^{-5}$
CRL8324**	$]10^{-5},10^{-6}[$	$>10^{-5}$	$>10^{-5}$	$>10^{-5}$	$>10^{-5}$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$	$]10^{-5},10^{-6}[$
CRL8422	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-5},10^{-6}[$	$]10^{-6},10^{-7}[$	$]10^{-6},10^{-7}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-6},10^{-7}[$
CRL8423	$]10^{-8},10^{-9}[$	$]10^{-8},10^{-9}[$	$]10^{-9},10^{-10}[$	$]10^{-9},10^{-10}[$	$]10^{-8},10^{-9}[$	$]10^{-8},10^{-9}[$	$]10^{-7},10^{-8}[$	$]10^{-7},10^{-8}[$	$]10^{-5},10^{-6}[$	$]10^{-7},10^{-8}[$	$]10^{-9},10^{-10}[$	$]10^{-7},10^{-8}[$

Inhibitory concentrations (M) flanking the value of the 50% inhibitory concentration of the compounds of formula I, II(*) or III(**) on the cell lines

Table III gives the results of the average IC_{50} values (in nM) (calculated from the cytotoxic activity on the 12 tumor lines studied) and the MTD/IC_{50} ratios (these ratios are calculated by forming the ratio of the MTD values and the IC_{50} values expressed as numbers without units).

TABLE III

Compounds CRL	IC_{50} (nM)	MTD/IC_{50}	MTD/IC_{50}*
CRL 8274 (Ascididemin)	100	0.20	1
CRL 8269 (2-bromoleptoclinidone)	120	0.33	2
CRL 8289 (Example 6)	10	2.00	10
CRL 8248 (Example 8)	80	2.00	10
CRL 8241 (Example 3)	140	1.14	6
CRL 8297 (Example 5)	90	1.78	9
CRL 8325 (Example 4)	37	4.32	22
CRL 8344 (Example 7)	53	3.02	15
CRL 8347 (Example 9)	21	7.62	38
CRL 8323 (Example 1)	60	0.33	2
CRL 8301 (Example 2)	270	0.59	3
CRL 8389 (Example 17)	420	0.38	2
CRL 8368 (Example 10)	480	0.33	2
CRL 8406 (Example 19)	60	2.67	13
CRL 8407 (Example 20)	22	7.27	36
CRL 8416 (Example 21)	80	2.00	10
CRL 8418 (Example 23)	110	0.37	2
CRL 8419 (Example 22)	60	0.67	3.3
CRL 8422 (Example 24)	100	1.60	8.3
CRL 8423 (Example 25)	7	22.86	114

*: the ratio MTD/IC_{50} for the various compounds was estimated by taking as reference a ratio equal to 1 for ascididemin.

The compounds described show, on the tumor cell line models, IC_{50} values (nM) which are greater than or equivalent to that of ascididemin. With the exception

of CRL 8289 (whose maximum tolerated dose is equivalent to that of ascididemin, but whose IC_{50} value is ten times lower than that of ascididemin), the maximum tolerated doses of the compounds described, considered by default as equivalent to 160 mg/kg, are markedly higher than those of ascididemin (20 mg/kg). These results suggest that this novel family of compounds have no direct toxicity. Consequently, the tolerance/cytotoxic activity ratios of the compounds illustrated in the present invention are markedly higher than that of the natural ascididemin. These compounds may thus be used as antitumor drugs, for their cytotoxic properties, at tissue concentrations that are higher than those induced with the natural ascididemin. They are thus characterized by better therapeutic manageability. CRL 8289, whose IC_{50} value is 10 nM, also shows better therapeutic manageability than ascididemin.

By virtue of their cytotoxic properties, the compounds of formulae I and Ia as described, or in the form of acceptable pharmaceutical salts or solvates, may be used as active principles of drugs.

The compounds of formulae I and Ia are generally administered in dosage units established either per m^2 of body surface or per kg of weight. Said dosage units are preferably formulated in pharmaceutical compositions in which the active principle is mixed with one (or more) pharmaceutical excipient(s).

The compounds of formulae I and Ia may be used, according to the cancer pathology of the individual to be treated, at doses of between 0.05 and 350 mg/m^2 of body surface, preferably at doses from 0.5 to 50 $mg/m^2/day$ for a curative treatment in the acute phase as a function of the number of treatment cycles of each cure. For maintenance treatment, the compounds of formulae I and Ia will advantageously be used at

doses from 0.05 to 25 $mg/m^2/day$ and preferably at doses from 0.1 to 1.5 $mg/m^2/day$ depending on the number of treatment cycles of the cure. They may be combined with antitumor drugs used in validated intensive multidrug therapy protocols.

In the pharmaceutical compositions of the present invention for oral or intravenous administration, the active principles may be administered in unit forms of administration, mixed with conventional pharmaceutical supports that are suitable for human therapy. The suitable unit forms of administration comprise oral-route forms such as tablets, which may be splittable, or gel capsules, implants and intravenous administration forms.

For a parenteral administration (intravenous infusion at a constant flow rate), sterile aqueous suspensions, sterile isotonic saline solutions or sterile and injectable solutions which contain pharmacologically compatible dispersants and/or solubilizing agents, for example propylene glycol, polyethylene glycol or a β-cyclodextrin, are used.

Thus, to prepare an aqueous solution for intravenous injection intended for an infusion performed over 1 to 24 h, it is possible to use a co-solvent: an alcohol such as ethanol, a glycol such as polyethylene glycol or propylene glycol, and a hydrophilic surfactant such as Tween 80.

When a solid composition in the form of tablets is prepared, a wetting agent such as sodium lauryl sulfate may be added to the micronized or unmicronized active principle, and the whole is mixed with a pharmaceutical vehicle such as silica, gelatin, starch, lactose, magnesium stearate, talc, gum arabic or the like. The tablets may be coated with sucrose, with various polymers or with other suitable materials, or

alternatively they may be treated such that they have sustained or delayed activity and such that they continuously release a predetermined amount of active principle.

A preparation as gel capsules is obtained by mixing the active principle with a diluent such as a glycol or a glycerol ester and by incorporating the mixture obtained into soft or hard gel capsules.

The active principle may also be formulated in the form of microcapsules or microspheres, optionally with one or more supports or additives.

The active principle may also be presented in the form of a complex with a cyclodextrin, for example α-, β- or γ-cyclodextrin, 2-hydroxypropyl-β-cyclodextrin or methyl-β-cyclodextrin.

The compounds of formulae I and Ia will be used in the treatment of most solid tumors on account of their powerful cytotoxic activities, in particular for treating cerebral tumors, lung cancers, ovarian and breast tumors, colorectal cancers, prostate cancers and testicular tumors.